

**NOT FOR PUBLICATION**

**UNITED STATES DISTRICT COURT  
DISTRICT OF NEW JERSEY**

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BAUSCH HEALTH COMPANIES INC.	:	
et al.,	:	
Plaintiffs,	:	Civil Action No. 16-9038 (SRC)
v.	:	
ACTAVIS LABORATORIES FL, INC.,	:	<b>OPINION</b>
Defendant.	:	

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**CHESLER, U.S.D.J.**

**INTRODUCTION**

Plaintiffs Bausch Health Companies Inc., Progenics Pharmaceuticals, Inc., Salix Pharmaceuticals, Inc., and Wyeth LLC (collectively, “Plaintiffs”) bring this action for patent infringement against Defendant Actavis Laboratories FL, Inc. (“Actavis.”) Plaintiffs own U.S. Patent No. 8,524,276 (“the ’276 patent”), which is listed in the Orange Book as protecting Plaintiffs’ oral methylnaltrexone bromide tablet formulation, marketed under the brand name Relistor®. Plaintiffs complain that, by filing Abbreviated New Drug Application (“ANDA”) No. 209615 with the United States Food and Drug Administration, Defendant has infringed the ’276 patent. A bench trial on both infringement and Actavis’ patent invalidity defenses to infringement was held for 4 days, beginning on May 6, 2019, and ending on May 9, 2019. Upon hearing the evidence presented at trial, this Court finds that Plaintiffs have proven that claim 2 is infringed, and Actavis has not proven that claims 2 and 5 of the ’276 patent are

invalid.

## **BACKGROUND**

Just before trial, the parties submitted the following stipulation, which the Court entered:

1. Plaintiffs will limit the asserted claims at trial to only claims 2 and 5 of the '276 patent.
2. Actavis stipulates that the manufacture, use, sale or offer for sale in the United States, or importation into the United States, of the products of Actavis's ANDA No. 209615 would infringe claim 5 of the '276 patent, except to the extent such conduct is permitted under the safe harbor of 35 U.S.C. § 271(e)(1). Plaintiffs and Actavis agree that this stipulation does not fully resolve the issue of liability, which is still subject to Actavis's invalidity defense as set forth in paragraph 3.
3. The only defense that Actavis will present at trial with respect to claim 5 of the '276 patent is that claim 5 is invalid for obviousness.
4. With respect to claim 2 of the '276 patent, in addition to obviousness, Actavis will present its defense of non-infringement at trial.
5. Actavis will limit its defense of invalidity based on obviousness to the following combinations: (1) Sanghvi '899, WO '352, 2006 Handbook; (2) Sanghvi '899, WO '352, 2006 Handbook, Remington 2006; (3) Sanghvi '899, WO '352, 2006 Handbook, Heimbecher '504.

MNTX is methylnaltrexone. SDS is sodium dodecyl sulfate; SLS is sodium lauryl sulfate; SDS and SLS are alternate names for the same compound. OIC is opioid-induced constipation. APC is apparent octanol/water partition coefficient. "Quaternary ammonium compounds" ("QAC") is a genus of chemical compounds of which MNTX is a species. A POSA is a person of ordinary skill in the pertinent art.

## **STIPULATED FACTS**

The parties stipulated to the following facts in the Final Pretrial Order ("FPO"):

28. Methylnaltrexone bromide is a pharmaceutically acceptable salt of

methylnaltrexone.

29. Sodium lauryl sulfate is an amphiphilic pharmaceutically acceptable excipient.

30. Sodium lauryl sulfate is a surfactant.

32. Sodium lauryl sulfate comprises a sulfate (—OSO<sub>3</sub>—) group.

33. Sodium lauryl sulfate is also known as sodium dodecyl sulfate.

61. Actavis Laboratories FL, Inc. submitted to the United States Food and Drug Administration (“FDA”) Abbreviated New Drug Application (“ANDA”) No. 209615 seeking approval to engage in the commercial manufacture, use or sale of methylnaltrexone bromide tablets for oral use (“Actavis’s ANDA No. 209615 product” or “Actavis’s generic methylnaltrexone product” or the like).

70. Actavis’s ANDA No. 209615 product contains 28.57% methylnaltrexone bromide by weight of the composition.

71. Actavis’s ANDA No. 209615 product contains 9.73% sodium lauryl sulfate by weight of the composition.

76. Dr. Elder conducted testing intended to replicate the test method that Dr. Koleng used to determine the apparent octanol/water partition coefficient for methylnaltrexone in Actavis’s ANDA No. 209615 product at a pH of about 1.1 and measured values of 0.051 and 0.053 respectively for two of Actavis’s tablets from Actavis’s ANDA No. 209615 exhibit batch lot number 4056R0013A.

77. Without conceding that the documents below anticipate or render obvious any of the claims of the ’276 patent, the following documents are prior art, as the term prior art is defined under 35 U.S.C. § 102:

- U.S. Patent Publication No. 2005/0004155 (“Boyd ’155”);
- U.S. Patent Publication No. 2004/0259899 (“Sanghvi ’899”);
- U.S. Patent Publication No. 2006/0009504 (“Heimbecher ’504”);
- PCT Publication No. WO 2004/091622 (“Boyd ’622”);
- PCT Publication No. WO 2008/121352 (“WO ’352”);
- PCT Publication No. WO 2009/137086 (“WO ’086”);
- Handbook of Pharmaceutical Excipients (Raymond C. Rowe et al. eds., 5th ed. 2006) (“2006 Handbook”);
- Aungst, B. J., Novel Formulation Strategies for Improving Oral Bioavailability of Drugs with Poor Membrane Permeation or Presystemic Metabolism, JOURNAL OF PHARMACEUTICAL SCIENCES, 82(10): 979-87 (1993) (“Aungst 1993”);

- Kararli, T. T. et al., Ionic Strength Dependence of Dissolution for Eudragit S-100 Coated Pellets, *PHARMACEUTICAL RESEARCH*, 12(11): 1813-16 (1995) (“Kararli 1995”);
- Meyer, J. D. et al., Hydrophobic Ion Pairing: Altering the Solubility Properties of Biomolecules, *PHARMACEUTICAL RESEARCH*, 15(2): 188-193 (1998) (“Meyer 1998”); and
- Remington The Science and Practice of Pharmacy (David B. Troy (*Id.* Matthew J. Hauber eds., 21st ed. 2006) (“Remington 2006”).

78. On April 24, 2008, the FDA approved an injectable Relistor® product, a single-use vial containing 12 mg/0.6 mL solution for subcutaneous injection, under NDA No. 021964 for the treatment of opioid-induced constipation in patients with advanced illness who are receiving palliative care, when response to laxative therapy has not been sufficient.

## **THE ISSUES FOR TRIAL**

1. Have Plaintiffs proven by a preponderance of the evidence that Defendants have infringed claim 2 of the '276 patent?
2. Has Defendant proven by clear and convincing evidence that claims 2 and 5 of the '276 patent are invalid as obvious, pursuant to 35 U.S.C. § 103?

## **THE EVIDENCE AT TRIAL**

What follows is selected excerpts from the testimony of the witnesses appearing in court at trial:

### **A. Testimony of John Koleng**

Dr. Koleng was qualified as an expert witness in the field of pharmaceutical formulation and drug delivery, product development and operations. (Tr. 80:5-12.) Dr. Koleng stated that the terms SDS and SLS are used interchangeably and refer to the same compound. (*Id.* 81:15-18.) The Actavis ANDA product satisfies the ion pair requirement in claim 2. (*Id.* 84:14-16.) Dr. Koleng directed testing of product samples conducted by a laboratory, SSCI. (*Id.* 86:17-23.)

SSCI tested product samples from Actavis's exhibit batches for ANDA number 209615. (Id. 88:4-6.) Three experiments were performed. (Id. 88:17.) In this case, an apparent octanol/water partition coefficient ("APC") is the ratio of the concentration of methylnaltrexone in the octanol phase and the concentration in the aqueous phase. (Id. 89:15-20.) SSCI used the shake-flask method for determining the APC, which is described in the '276 patent. (Id. 90:2-3.)

In the first experiment, testing of the three exhibit batches produced APC results of .936, .944, and 1.0. (Id. 91:15-21.) Testing of the methylnaltrexone bromide alone produced an APC of .002. (Id. 92:1-4.) These results show a dramatic increase in the APC for the Actavis tablets compared to the APC for the methylnaltrexone bromide alone. (Id. 92:11-14.) Dr. Koleng concluded from this increase that an ion pair had formed between the MNTX and SLS in solution. (Id. 92:19-22.) The shake-flask method is well-suited to determining the APC of a composition which includes a pure compound. (Id. 93:15-20.)

In the second experiment, SSCI created a "tablet blend" that duplicated the composition of the Actavis tablet product, but without SLS. (Id. 95:2-7.) SSCI ordered the raw materials from the same vendors or manufacturers that Actavis had specified. (Id. 96:1-6.) SSCI measured an APC of .01 for the tablet blend without SLS. (Id. 99:5-7.) This test, compared to the results from the first study of the tablets, shows a dramatic increase in the measured APC when SLS is present. (Id. 99:15-18. Dr. Koleng concluded that the increase in APC is the result of ion pairing between MNTX and SLS. (Id. 99:23-100:3.) The increase in APC is not due to any other components in the Actavis composition. (Id. 100:8-11.)

In the third experiment, SSCI used the shake-flask procedure with the Actavis exhibit

batch tablets, but measured the resultant concentration of MNTX and SLS in the octanol phase. (Id. 101:4-8.) The results confirm that, in the Actavis ANDA product, the MNTX and SLS form an ion pair. (Id. 101:18-22.) Dr. Koleng concluded that the Actavis ANDA product infringed claim 2. (Id. 101:23-25.)

On cross-examination, Dr. Koleng stated that, prior to being retained by Plaintiffs, he had never used the shake-flask method to determine the APC for an active pharmaceutical ingredient within a tablet. (Id. 102:17-23.) He was not aware of any prior art reference in which the shake-flask method was used to determine the APC of an active ingredient within a tablet. (Id. 103:8-14.) The studies conducted by SSCI used the shake-flask method defined in Example 4 of the '276 patent. (Id. 103:15-22.) Example 4 of the patent discloses a method used to determine the APC of pure compounds and not tablets. (Id. 104:13-25.) The table in Example 4 shows results for three single active pharmaceutical ingredients. (Id. 105:10-24.) Thus, the only disclosure in the patent that describes finding an APC for MNTX and SLS tests a salt which has combined the two components. (Id. 106:10-20.)

Other than in this litigation, Dr. Koleng had never determined whether an ion pair had formed in a solution. (Id. 108:18-21.) Outside of the patent itself, he did not consult any literature about determination of ion pairing in solution. (Id. 110:23-111:3.) Dr. Koleng did not draft, approve, or review the protocol for the second experiment before it was conducted; rather, he read the final report of the experiment. (Id. 112:7-24.) He was involved in the drafting and approval of the protocols for the first experiment. (Id. 113:7-13.) For the tablet blend experiment, Dr. Koleng agreed that he could have asked SSCI to make tablets containing the Actavis ANDA ingredients except for SLS. (Id. 114:13-15.) He did not do a literature

search to see if there were mechanisms other than ion pairing that could be responsible for increasing the APC in the experiments that were conducted. (Id. 116: 3-7.) Actavis' tablets contain excipients other than SLS that could potentially affect the APC of MNTX. (Id. 116:14-19.) The MNTX and SLS in the Actavis tablets will not always form ion pairs in solution, depending on the formulation. (Id. 118:25-119:6.) The SSCI experiments were performed at a particular pH, and Dr. Koleng could not say what would happen at another pH. (Id. 119:13-18.) SSCI did not determine the amount of any other excipients in the Actavis tablet that had partitioned into the octanol phase. (Id. 124:21-25.) Comparing the measured APC of MNTX alone, .002, with the measured APC of the modified tablet blend without SLS, .01, the difference could have resulted from any sort of interaction in the tablet. (Id. 128:8-129:3.) Dr. Koleng did not know whether the increase was due to ion pairing or some other interaction. (Id. 129:14-20.)

After the examination finished, the Court asked Dr. Koleng why he concluded that the increase in APC in the first experiment was evidence of ion pairing, but he did not know about the cause of the increase in APC in the second experiment. (Id. 135:1-20.) Dr. Koleng explained that his conclusion in the first experiment was “derived from the teaching and the specification of the ’276 which specifically describes that in the presence of – when methylnaltrexone and lauryl sulfate come together from a composition in solution, they form an ion pair and that results in increase in the lipophilicities of methylnaltrexone which then allows it to partition into the oil phase which is quantified as an increase in APC.” (Id. 135:22-136:4.)

#### **B. Testimony of Walter Chambliss**

Dr. Chambliss was qualified as an expert in the fields of pharmaceutical sciences and

pharmaceutical formulations. Dr. Chambliss did not agree with Dr. Koleng that Actavis' ANDA product infringed claim 2. (Id. 148:11-17.) The testing method used was flawed and the results were unreliable. (Id. 150:4-6.) In over 30 years of work, Dr. Chambliss had never seen anyone run this kind of test on a tableted formulation, nor did Dr. Koleng cite a single reference in which that was done. (Id. 150:9-16.) One cannot use the APC test to determine whether two substances in a tablet form an ion pair in solution. (Id. 153:9-11.) Nor can running this test on a tablet even determine the APC. (Id. 154:2-8.) Example 4 in the patent tested a pure compound, which is what the test is used for. (Id. 154:13-19.) The Actavis ANDA formulation contains about 40% insoluble components, which will just float around during a shake-flask test, which could impact the results. (Id. 156:17-25.)

Dr. Chambliss said that Dr. Koleng used scientifically inappropriate comparisons when he compared the APC for MNTX alone with the APC for the Actavis tablet. (Id. 160:6-18.) When SSCI created the tablet blend without SLS, they did not use all of the excipients in the Actavis formulation. (Id. 161:6-8.) The tablet blend without SLS that SSCI made and used was not representative of the ANDA product without SLS. (Id. 161:19-21.) The scientifically appropriate comparison would have been to compare a tablet without SLS to a tablet with SLS. (Id. 162:11-19.) To make the comparison more appropriate, they could have compared the tablet blend with SLS to the actual Actavis tablet with SLS. (Id. 163:2-10.) The data in the patent is inconsistent with the data that SSCI generated. (Id. 164:22-23.) SSCI reported an APC for MNTX of .002, while the patent reported a value of .025. (Id. 165:1-12.) Another inconsistency is that Example 4 reports an APC for methylnaltrexone lauryl sulfate salt in solution of 32, while SSCI reported a value of 1. (Id. 166:5-25.) Dr. Chambliss stated that

these results are evidence of no ion pairing occurring, because the value SSCI obtained is so far off from the value stated in the patent. (Id. 167:1-8.) Had there been ion pairing, the APC value SSCI measured should have been much higher. (Id. 168:23-169:3.)

Dr. Chambliss stated that he reviewed the testing done by Dr. Elder, who attempted to replicate SSCI's testing method at different pH levels. (Id. 170:7-10.) Dr. Elder obtained an APC of .05, so both SSCI and Dr. Elder obtained results that are much lower than what would be expected from the teaching of the patent. (Id. 172:5-19.) None of this evidence shows that the Actavis ANDA product infringes claim 2. (Id. 172:20-23.)

Dr. Chambliss stated that claims 2 and 5 are obvious in view of the prior art. (Id. 173:3-4.) Dr. Chambliss stated: "The FDA had approved a subcutaneous formulation of methylnaltrexone bromide in 2008 under the trade name of Relistor. Oral formulations containing methylnaltrexone were known in the art, and methylnaltrexone was known to have permeability issues." (Id. 174:6-10.) Patients prefer oral formulations to injections. (Id. 174:22-24.) The POSA would have been motivated to develop an oral formulation of MNTX. (Id. 175:5-9.) There are three main types of solid oral formulations: 1) immediate release; 2) delayed release/enteric coating; and 3) extended release, which combines the features of 1 and 2. (Id. 175:15-176:2.) The POSA in March of 2010 would have selected an immediate release formulation of MNTX, because it provides the fastest relief, which is desirable for the treatment of constipation. (Id. 176:3-14.) The POSA would not have selected an enteric-coated formulation because none of the three main reasons to do so applied: 1) to protect the drug, if it is unstable in stomach acid; 2) to protect the stomach from upset caused by the drug; and 3) to deliver the drug to a site lower down the GI tract. (Id. 177:8-21.)

Sanghvi '899 discloses methods of treating constipation with oral formulations of MNTX in all three types (immediate, delayed, extended.) (Id. 178:5-17.) It disclosed an immediate release formulation that lacked any ingredient to address the known permeability problem of MNTX, so the POSA would be motivated to find an ingredient to address that. (Id. 179:18-23.) Drugs with permeability problems are mostly washed through the GI tract. (Id. 181:1-9.) The poor permeability of MNTX was well-known in the art. (Id. 183:21-23.) Yuan 1997 states that MNTX has lower lipid solubility and does not cross the blood-brain barrier, and thus could have poor permeability in the GI tract. (Id. 184:18-185:1.) Yuan reported that very high oral doses of MNTX did not produce high blood levels, showing poor permeability. (Id. 185:16-186:7.)

Dr. Chambliss stated that the POSA would have understood the Accordingly Phrase<sup>1</sup> to mean that it is obvious that you need to improve the bioavailability of MNTX. (Id. 187:7-13.) Aungst 1993 is a review article which summarized publications on the subject of improving bioavailability of drugs with poor membrane permeation or presystemic metabolism. (Id. 188:12-189:4.) In Aungst 1993, Table 1 is titled, “categories of oral bioavailability problems and then possible solutions.” (Id. 189:8-10.) Table 1 shows different reasons for poor bioavailability, and one is poor membrane permeation; the possible solutions are permeation enhancers, ion pairing, complexation, and lipid or surfactant vehicles. (Id. 189:14-24.) A POSA might implement these strategies by looking for an excipient that is a permeation enhancer. (Id. 190:18-24.) Based on a number of considerations, a POSA would have selected SLS as an excipient for MNTX. (Id. 191:6-12.) Dr. Chambliss said that he had previously

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<sup>1</sup> “Accordingly, the need exists for bioavailable oral dosage formulations comprising methylnaltrexone.” ‘276 patent, col.2 ll.61-62 (hereinafter, the “Accordingly Phrase.”)

used SLS in many, many oral formulations. (Id. 191:13-16.) The 2006 Handbook was the world-recognized source on pharmaceutical excipients, and it has a chapter on SLS. (Id. 191:24-193:1.) In that chapter, the 2006 Handbook says that SLS is “an anionic surfactant used in tablets as a lubricant, and also used as a wetting agent, which is another term for surfactant.” (Id. 193:5-8.) It also says that “sodium lauryl sulfate is an anionic surfactant employed in a wide range of nonparenteral pharmaceutical formulations.” (Id. 193:14-17.) The POSA would have had no safety concerns about using SLS in an oral pharmaceutical product, based on the 2006 Handbook. (Id. 194:22-25.) The Handbook also states that SLS is GRAS listed (“Generally Regarded As Safe”) and included in the FDA Inactive Ingredients Guide. (Id. 195:8-25.) The Inactive Ingredients Guide would have taught the POSA that SLS was commonly used in pharmaceutical products, including oral formulations, up to 50 mg in a tablet. (Id. 204:7-12.)

Whitehead 2007 is titled, “Safe and effective permeation enhancers,” and studied 51 enhancers. (Id. 205:5-18.) Of these 51, five were anionic surfactants, and SLS was ranked as the most safe and effective of the anionic surfactants. (Id. 205:22-206:14.) Whitehead also stated that, of the ten safest and most effective permeation enhancers, SLS was one of three that had been previously analyzed for oral delivery. (Id. 206:25-207:16.) Of those three, SLS is the only anionic surfactant. (Id. 207:19-124.) The POSA would understand Whitehead 2007 to teach that SLS is an obvious choice as a permeation enhancer for a MNTX formulation. (Id. 208:1-6.)

WO ‘352 was published in 2008 and describes the classes of excipients that could be used with MNTX. (Id. 208:17-209:11.) It includes SLS in the list of lubricants. (Id. 209:15-

16.) The POSA who read this reference would expect that one could add SLS to a tablet formulation and it would be compatible with MNTX. (Id. 210:4-9.) The POSA would have been motivated to select SLS for use as a permeation enhancer in an oral MNTX formulation. (Id. 212:13-22.) The POSA would either have made the MNTX-lauryl sulfate salt, or added SLS to the MNTX formulation. (Id. 213:1-7.)

As to claim 5, Dr. Chambliss stated that the subject matter would have been obvious as of March 2010, in view of 2006 Handbook, WO '352, and Sanghvi '899. (Id. 214:5-215:20.) The dissolution limitation would have been obvious because it requires routine conditions that have been known for decades. (Id. 215:21-216:15.) Remington 2006, a well-known pharmaceutical treatise, teaches dissolution testing of immediate release formulations that targets 85% dissolution in 15 minutes. (Id. 216:20-218:23.)

As to claim 2, a formulator who used MNTX and SLS in a composition would expect ion pairing to occur in solution. (Id. 219:14-23.) Use of the MNTX-lauryl sulfate salt “enhance[s] the chances of maybe ion pairing would occur.” (Id. 219:23-220:4.) Dr. Chambliss said that he does not know whether ion pairing would be expected if SLS were added as an excipient, rather than using the MNTX-lauryl sulfate salt. (Id. 224:15-20.) Using the MNTX-lauryl sulfate salt, “you are giving it the best chance. You are starting with the salt that is bonded together and then you are hoping it's going to stay close enough together when it dissociates that ion pairing could occur.” (Id. 225:4-7.) Heimbecher '504 teaches ion pairing using a lauryl sulfate salt, but not with MNTX. (Id. 226:2-16.) The POSA would understand from Heimbecher '504 that, if you wanted to increase your chances of having ion pairing, you would form a salt with the active ingredient. (Id. 226:22-227:1.) Thus, claim 2 would have been obvious. (Id. 227:13-17.)

On cross-examination, Dr. Chambliss stated that the prior art recognized that ion pairing was controversial, and that he would not know whether MNTX and SLS would ion pair in any formulation without doing a test. (Id. 233:6-17.) The formation of an ion pair only occurs if the ions are close enough in solution for an electrostatic attraction, and Dr. Chambliss does not know what proximity is necessary for formation of ion pairs in solution. (Id. 233:19-25.)

Heimbecher '504 does not disclose any quaternary ammonium compound or APC coefficient. (Id. 235:16-22.) The POSA formulating an oral methylnaltrexone formulation would look to other quaternary ammonium salts. (Id. 237:7-10.) The effect of a surfactant on drug absorption is highly dependent on the drug being studied. (Id. 239:4-7.) Increasing partitioning does not always increase permeability. (Id. 241:22-24.) Aungst 1993 teaches that, in many instances, the design of membrane permeation properties into an active compound – for example, MNTX-lauryl sulfate – may be more likely to succeed in improving permeation than permeation approaches. (Id. 256:8-17.) SLS is an n-alkyl sulfate. (Id. 257:2-4.)

### **C. Testimony of Stephen Davies**

Dr. Davies was qualified as an expert in the field of chemistry. Dr. Davies stated that SLS is a long chain, 12-carbon chain compound, and is the same as SDS. (Tr. 296:19-25.) The 12 refers to the number of carbon atoms in a straight chain. (Id. 297:5-6.) “Ion-pairing is where in solution a positive charge comes close to a negative charge and the interaction between the forces, between those two charges are able to hold it together for some substantial period of time so that they form what it says, a pair of ions, positive one next to a negative one.” (Id. 301:13-20.)

Dr. Davies disagreed with Dr. Chambliss' opinions regarding Heimbecher '504, which

does not relate to quaternary ammonium compounds. (Id. 306:25-307:6.) A POSA would not find Heimbecher '504 relevant at all to quaternary ammonium compounds. (Id. 307:22-25.) The teachings of Heimbecher '504 about ion pairing involve different forces than those at work in the ion pairing in this case. (Id. 308:3-9.) Paragraph 84 of Heimbecher '504 deals with ion pairs with sodium docusate, not SLS. (Id. 308:10-24.) A salt in solution may or may not form an ion pair. (Id. 309:15-310:3.) It makes no difference, in terms of the likelihood of forming an ion pair, whether one preformed salt is put in solution, or the ions come from separate salts. (Id. 310:4-7.) Ion pairing is not a common phenomenon; the Quintanar-Guerrero reference shows that ion-pairing is unpredictable and doesn't happen all the time. (Id. 312:15-25.) The Takacs-Novak reference says that the concept of ion pairing has been hotly debated in the pharmaceutical literature. (Id. 314:22-315:1.) Takasz-Novak studied quaternary ammonium compounds, but not with any sulfate counter ions, and found that you can't predict which quaternary ammonium salts will ion pair or under what conditions. (Id. 315:10-317:1.) A POSA would not understand the term "sulfate salts," as used in paragraph 36 of Sanghvi '899, to include SLS; the POSA would expect "alkyl sulfates" to include lauryl sulfate. (Id. 335:3-6.)

A POSA who wanted to increase the lipophilicity of MNTX could have used one of a very large number of carboxylic acids and make esters from them. (Id. 335:10-24.)

On cross-examination, Dr. Davies stated that Example 4 in the '276 patent does not state that an MNTX-lauryl sulfate salt is an ion pair; it describes a process in which that salt is put in solution and forms ion pairs. (Id. 340:7-21.) The data in the table at the bottom of Example 4 shows an increase in the APC, which the POSA would understand to mean that ion pairs are forming. (Id. 342:5-10.) Dr. Davies stated that he could not think of any other explanation for

why there would be an increase in APC other than ion pairing; it is the standard way to show ion pairing. (Id. 342:18-25.) As to the Bouchard 2001 reference and the role of the Galvani potential difference, Dr. Davies stated that, as he said in his expert report, Bouchard 2001 applies to situations in which there is an excess of anion present, which is not the case here. (Id. 346:6-347:21.) While SLS is a lipophilic anion, it is not in excess here. (Id. 348:2-5.) “The Galvani potential won’t be there if there’s not an excess of anion.” (Id. 349:7-8.) The standard method for determining ion pair formation is the shake-flask method. (Id. 349:24-350:1.) The statement in Lombardo 2008 about the Galvani potential difference refers to Bouchard 2001 and the POSA would know that this applies only with an excess of anion present. (Id. 351:8-352:7.)

On redirect examination, Dr. Davies said that the concept of Galvani potential difference is not an accepted explanation for an apparent partition coefficient increase, and that he had not come across this hypothesis other than in the papers just discussed. (Id. 358:12-17.)

#### **D. Testimony of Richard Rauck**

Dr. Rauck was qualified as a medical expert in the field of pain management and in the treatment of the side effects of pain management, including opioid-induced constipation. Before March of 2010, both immediate release and enteric-coated forms of oral MNTX were known in the art. (Id. 375:6-12.) In prior art clinical studies, efficacy in the treatment of opioid-induced constipation was measured in terms of time to laxation and oral-cecal transit time, a measure of time for a substance to go from ingestion to the cecum. (Id. 376:2-18.) The prior art clearly favored enteric-coated formulations of MNTX. (Id. 376:19-25.) The enteric-coated formulations had an effect with a lower dose. (Id. 377:1-8.) Moss 2008 is a review article that summarizes the state of the art in 2008. (Id. 378:4-6.) Moss 2008 states that, with

an immediate release form, 19.2mg/kg were required to completely reverse intestinal transit delay; with an enteric-coated preparation, the same effect was achieved with a dose of 3.2mg/kg, which is 1/6 of the dose. (Id. 378:14-23.) “Because the enteric-coated preparation had this greater potency and less systemic bioavailability than the non-enteric-coated or immediate-release formulation, it was felt that this was consistent with a local site of action, that being a site of action in the colonic lumen.” (Id. 378:25-379:4.) Higher blood levels of a drug are generally associated with a greater incidence of side effects. (Id. 379:19-20.) The prior art knew that intravenous MNTX reduced OIC, but it had some side effects. (Id. 380:8-16.) Foss ‘591 teaches that high levels of methylnaltrexone in the plasma can lead to undesirable effects such as orthostatic hypotension. (Id. 381:2-7.) A POSA developing an oral formulation would have wanted to keep plasma levels low to prevent orthostatic hypotension. (Id. 382:22-383:2.) Dr. Rauck reviewed a clinical study which compared an immediate-release form of MNTX with SLS to one without SLS, and the formulation with SLS was dramatically and unexpectedly superior in terms of time to laxation. (Id. 383:3-25.) This is clinical study 1115, which was confidential and not in the prior art. (Id. 384:9-15.) The formulation with SLS was found to be ten times faster, in terms of median time to first laxation, than the formulation without SLS. (Id. 389:4-15.) The formulation with SLS shows a dramatic improvement in efficacy. (Id. 393:10-11.)

Clinical study 105 compared enterically-coated spheroids in capsules to enterically-coated tablets. (Id. 395:15-25.) Both formulations had dosages of 300 mg MNTX without SLS. (Id. 396:11-24.) Clinical study 105 was a confidential study and not in the prior art. (Id. 397:3-8.) Comparing studies 105 and 1115, the immediate release formulations with SLS were

dramatically superior to either enterically-coated formulation. (Id. 400:1-6.) In view of the prior art, these superior results were unexpected. (Id. 401:25-402:3.) Based on the prior art, the enteric-coated formulations would have been expected to have equal or better efficacy at a significantly lower dose. (Id. 402:15-18.)

#### **E. Testimony of Robert Williams**

Dr. Williams was qualified as an expert in the field of the design, evaluation, and formulation of drug products encompassing pharmaceutical formulation and pharmaceutical development. Dr. Williams stated that a POSA would understand the dissolution conditions in claim 5 to describe an immediate release tablet. (Id. 434:18-25.) Sanghvi '899 discloses oral formulations of MNTX: an immediate-release tablet, an enteric-coated tablet, and a sustained-release tablet. (Id. 445:19-447:5.) The prior art described enteric release formulations as providing as good or better therapeutic performance than an immediate-release methylnaltrexone dosage form at much lower dose. (Id. 448:2-6.) The prior art taught that blood levels of MNTX do not correspond to the clinical endpoint, so the prior art did not teach about bioavailability. (Id. 448:7-14.)

Dr. Williams disagreed with Dr. Chambliss' opinion that a POSA would have been motivated to improve the absorption and bioavailability of oral formulations of MNTX. (Id. 452:9-15.) Given that the prior art taught that the therapeutic endpoint is not related to blood levels, a POSA would not have the goal of increasing absorption and bioavailability. (Id. 452:17-23.) Kakemi studied use of SLS with three quaternary ammonium compounds and found that, even though the APC increased, there was no observed increase in absorption. (Id. 453:18-454:6.) Langguth studied a series of alkyl sulfates and a quaternary ammonium

compound, trospium, looking at the effect of the number of carbons in the chain length of the alkyl sulfate with the lipophilicity and apparent partition coefficient and flux, and found that maximum membrane permeation occurred for counter ions of medium chain length, 7 or 9, and that outside of this range, permeation is little different from the original compound. (Id. 454:17-455:20.) A POSA would understand from Langguth that SLS would not be as effective with trospium as medium chain length alkyl sulfates would be, with a chain length of 7 or 9. (Id. 455:21-456:5.) In the notice of allowance of the '276 patent, the examiner referred to Langguth. (Id. 456:17-457:13.) Table 4 in Aungst 1993 cites reference 48 in regard to alkyl sulfates and trospium, and reference 48 is Langguth. (Id. 458:1-14.)

In Table 1, the van Hoogdalem reference discloses classes of enhancers for intestinal drug absorption, including SLS. (Id. 462:16-463:1.) Van Hoogdalem found that the effects of surfactants on drug absorption appeared to be correlated with the occurrence of adverse affects on mucosal integrity. (Id. 464:9-16.) In stating conclusions, van Hoogdalem presented a group of compounds that were first choice for further study, based on safety and effectiveness; SLS was not in that group. (Id. 465:19-466:8.)

A skilled pharmaceutical formulation scientist would be skeptical about using permeation enhancers, including SLS, in oral formulations of SLS. (Id. 469:3-12.) The safety concerns about SLS stated in the 2006 Handbook are not limited to the bulk material. (Id. 470:10-471:5.) Based on Kakemi and Langguth, a POSA would not have expected SLS and MNTX to work. (Id. 473:2-20.) The results of study 1115 would have been unexpected to the POSA. (Id. 474:9-15.)

On cross-examination, Dr. Williams agreed that permeability is the ability of a drug to

access an intestinal cell, and said that lipid solubility is an indicator of permeability. (Id. 484:1-8.) The POSA would know that SLS had been used as a permeation enhancer. (Id. 485:5-8.) Dr. Williams agreed with the inventors' statement that SLS was currently used in many marketed products with known daily dose limits. (Id. 493:2-8.) By 2010, the technique of using ion pairing to improve bioavailability was established in the industry and would have been considered a conventional technique. (Id. 500:1-10.) Dr. Williams agreed that there are possibly other mechanisms responsible for an increase in APC, in addition to ion-pairing. (Id. 507:3-6.) APC measures can vary with pH. (Id. 507:11-13.) The Yuan 2000 reference reported a study of an enteric MNTX formulation, and this study is cited in the review paper by Moss. (Id. 510:2-17.)

#### **F. Testimony of David Taft**

Dr. Taft was qualified as an expert in the fields of pharmaceutics (but not formulations), pharmacokinetics, and pharmacodynamics. Dr. Taft stated that "the first step for a drug to be bioavailable is it has to be able to permeate into the intestine itself." (Tr. 540:2-3.) "When I define bioavailability, I don't define it as absorption into the bloodstream." (Id. 541:12-13.) "It's well-known in the field that there are therapeutic classes of medications where the drugs work locally in the GI tract but don't have necessarily bioavailability." (Id. 543:12-15.) A drug like MNTX has to be in solution in the GI fluids and then permeate into the intestine to reach its site of action. (Id. 550:20-25.) The prior art taught six general things about MNTX: 1) despite low bioavailability; oral MNTX was effective; 2) plasma levels should be kept low because of side effects like orthostatic hypotension; 3) no correlation between plasma levels and efficacy; 4) MNTX is sufficiently permeable as to be effective; 5) the main site of action is in the GI tract;

and 6) enteric-coated oral MNTX is preferred because you get equal or superior activity at a lower dose. (Id. 556:17-558:12.)

Yuan 1997 would not motivate the POSA to increase permeation of MNTX, because it found no correlation between effectiveness and plasma levels. (Id. 564:3-14.) The permeability of MNTX is sufficient because of its potency. (Id. 567:5-17.)

As to the Accordingly Phrase, the POSA would understand it to reflect that the inventors “started with the prior art best-performing formulation, and unexpectedly found that it didn't work.” (Id. 575:3-16.) The prior art taught that bioavailability was not a problem for oral MNTX. (Id. 575:17-18.) The inventors did not improve the bioavailability of MNTX by using SLS. (Id. 575:22-24.) The 1115 study shows that, in “a head-to-head comparison of the bioavailability of an oral formulation without SLS to an oral formulation with SLS, . . . the bioavailability was not different.” (Id. 576:1-9.)

There were experiments in the prior art that were designed to evaluate the effect of SLS on the absorption of quaternary ammonium compounds, and showed that SLS did not work to improve the absorption of quaternary ammonium compounds. (Id. 579:11-23.) Langguth showed that compounds with larger carbon chains were too big, and that the ideal was a compound with a chain length range of seven to nine. (Id. 580:9-24.)

Dr. Taft disagreed with Dr. Chambliss about the Whitehead 2007 reference. (Id. 581:18-25.) Whitehead used mannitol as a test compound, which is not a quaternary ammonium compound. (Id. 582:2-4.) Whitehead highlighted the use of PPZ, not SLS. (Id. 583:13-23.) Dr. Taft also disagreed with Dr. Chambliss that the POSA would have wanted to use a permeation enhancer with MNTX, because the prior art did not teach that bioavailability or

permeation was a problem for oral MNTX. (Id. 585:8-18.)

Aungst 1993 reviews potential approaches to improving bioavailability that a POSA might consider. (Id. 589:5-10.) In discussing approaches, Aungst states: “In many instances, the design of the membrane permeation properties directly into the active compound may be more likely to succeed in improving permeation and formulation approaches.” (Id. 591:7-15.) Aungst also discusses ion pairing and, regarding the examples of studies in Table IV, says that in most of these studies, referring to Table 4, the formulation was administered directly onto the absorbing surface of the intestine. Under these conditions, there is less tendency for the ion pairs to dissociate compared to when dosed orally because there is less dilution, and less dispersion and dissociation by other counterions in the GI tract. (Id. 592:20-593:6.)

Aungst 2000 states: The drug and the absorption promotor must be delivered to the absorption site simultaneously and a sufficient concentration of the absorption promoter must be achieved and maintained there. (Id. 594:17-595:7.) Kakemi and Langguth put the drug directly at the intended site of absorption, closed it off and left it there. (Id. 595:17-22.) It has happened that the bioavailability of a drug with an enhancer is profoundly lower after oral dosing than after administration directly to the intestine. (Id. 596:17-19.) Kakemi and Langguth taught that, for quaternary ammonium compounds, SLS didn’t work; this taught away from using SLS as a permeation enhancer. (Id. 597:11-17.)

On cross-examination, Dr. Taft agreed that, in the prior art, Yuan 2000 Enteric was the only enteric study. (Id. 603:17-24.) Dr. Taft stated that he had not seen any prior art enteric study that reported data about time to laxation. (Id. 603:25-604:4.) Yuan 2000 research letter was the one prior art study that reported time-to-laxation data. (Id. 604:10-17.) The Yuan

2000 research letter (“Yuan 2000 RL”) was an immediate release study that came after the enteric study by the same research group. (Id. 607:15-20.) Yuan 2000 RL measured time to laxation. (Id. 609:2-6.) Dr. Taft understood bioavailability in terms of amount of drug in the plasma. (Id. 612:24-613:2.)

The 1115 study clearly shows the inventors developed an effective formulation with SLS, but it was not due to increased bioavailability. (Id. 633:20-22.) The formulation did not increase bioavailability. (Id. 636:15-16.) The goal was to avoid potential side effects by reducing systemic levels. (Id. 636:23-637:2.)

#### **G. Testimony of Walter Chambliss on rebuttal**

Dr. Chambliss said that the POSA would know that *in vitro* studies, using the Caco-2 cell, are frequently and routinely used to determine the permeability of almost every compound. (Id. 648:20-24.) Dr. Chambliss did not agree that the prior art would have led a POSA to prefer an enteric-coated MNTX tablet to an immediate release tablet as of March 2010. (Id. 649:11-17.) The POSA, reading Moss 2008, would have thought “that oral delivery formulations that had been tested so far are not effective and they need to come up with a better oral delivery system.” (Id. 651:14-21.) The only issue that was preventing the development of a safe and effective oral formulation was the permeability issue of the MNTX. (Id. 653:6-9.) One would have wanted to come up with a formulation that addresses that problem, and an immediate-release formulation to get as fast an onset of action as possible. (Id. 653:10-13.)

A POSA would consider a lauryl sulfate to be a sulfate salt. (Id. 656:20-21.) Dr. Chambliss did not agree that Table 2 in the Takács-Novák reference teaches that an excess of counterions is required for ion pairing. (Id. 660:6-15.) That Table shows that, at a 1:1 ratio,

there is a three-times enhancement of lipophilicity, on average. (Id. 661:16-23.) Dr. Chambliss did not agree that it was unexpected that SLS would increase the effect of an oral MNTX tablet. (Id. 662:6-12.) This is because the formulations in clinical studies 105 and 1115 were not in the prior art, nor representative of the closest prior art, and because the improvement in efficacy from the addition of SLS would have been expected. (Id. 662:16-663:1.)

Generally, one would not make an enteric formulation unless one needed to, especially for a laxative, where an enteric coating would keep the tablet in the stomach for several hours before the possibility of any effect. (Id. 664:22-665:2.)

## **DISCUSSION**

Claims 2 and 5 of the '276 patent, which depend from independent claim 1, are at issue:

1. A pharmaceutical composition for oral administration comprising a solid dosage of (i) methylnaltrexone, or a pharmaceutically acceptable salt thereof, and (ii) sodium dodecyl sulfate (SDS), wherein the composition is a tablet, and wherein the composition comprises from about 7% to about 75% methylnaltrexone cation and dodecyl sulfate anion, based upon the total weight of the composition.
2. The pharmaceutical composition of claim 1, wherein the methylnaltrexone, or a pharmaceutically acceptable salt thereof, and sodium dodecyl sulfate (SDS) form an ion pair when dissolved in solution.
5. The pharmaceutical composition of claim 1, wherein at least 50% of the composition dissolves in a dissolution apparatus with paddles at 100 rpm in 900 mL of 0.1 N HCl at 37° C. within about 15 minutes.

The '276 patent descends from provisional application No. 61/313,018, filed on March 11, 2010 (the “Critical Date.”)

### **A. Patent invalidity: obviousness**

The Federal Circuit has summarized the fundamental principles of the law of obviousness as follows:

Under § 103, a patent may not issue “if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.” 35 U.S.C. § 103 (2006). Obviousness is a question of law based on underlying factual determinations, including: (1) the scope and content of prior art; (2) differences between prior art and claims; (3) the level of ordinary skill in the art; and (4) objective indicia of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18, 86 S. Ct. 684, 15 L. Ed. 2d 545 (1966). A party asserting that a patent is obvious must demonstrate by clear and convincing evidence that a skilled artisan would have had reason to combine the teaching of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success from doing so.

Par Pharm., Inc. v. TWi Pharm., Inc., 773 F.3d 1186, 1193 (Fed. Cir. 2014).

The parties agree on many basic facts. In the relevant art, prior to the Critical Date, MNTX was known as an opioid receptor antagonist useful as a pharmaceutical for the treatment of OIC. The “Background of the Invention” section of the ’276 patent recites the following key points in the history of MNTX, which has been studied since the 1970s. ’276 patent, col.1 ll.62-3. U.S. Patent No. 6,559,158 (the “’158 patent”), filed in 2000, claims use of MNTX for the treatment of OIC, including in an oral enterically-coated dosage form. The ’158 specification reports a study in which intravenous administration of MNTX to patients with OIC produced immediate laxation. ’158 patent, col.8 ll.52-64. The ’276 specification also reports that MNTX subcutaneous injection has been clinically approved in the United States, and the specification reports that certain subcutaneous doses induced laxation within four hours in a significant number of patients treated. ’276 patent, col.2 ll.19-26.

The ’276 patent then summarizes a number of prior art references dealing with oral dosage forms of MNTX. U.S. Patent No. 6,419,959 (the “’959 patent”) disclosed a controlled-release oral dosage form, designed to deliver MNTX across the entire GI tract, but did not report

data about the efficacy of the formulation. '276 patent, col.2 ll.27-41. U.S. Patent No. 6,274,591 (the “‘591 patent”) claimed a method of treating OIC by orally administering an enteric-coated MNTX dose, but did not report data about time to laxation. '276 patent, col.2 ll.42-49. The '158 patent claims, *inter alia*, both enterically-coated and immediate release oral dosage forms, and reported a study of the immediate release oral dosage form in which the fastest response was found in the subjects receiving the highest dose, with an average time to laxation of about five hours. '276 patent, col.2 ll.50-60.

After setting forth this background to the invention, the '276 specification states the Accordingly Phrase: “Accordingly, the need exists for bioavailable oral dosage formulations comprising methylnaltrexone.” '276 patent, col.2 ll.61-62.

### **1. The motivation to combine MNTX and SLS**

Because both claim 2 and claim 5 are dependent claims, and both depend on independent claim 1, to prove that either claim 2 or claim 5 is obvious requires proof that claim 1 is obvious. This Court thus begins its obviousness inquiry with claim 1, which covers the combination of MNTX and SLS in a tablet for oral administration. Actavis builds its obviousness case from the following propositions: 1) all the elements of the asserted claims were in the prior art; 2) a POSA would have been motivated to combine MNTX and SLS in a tablet, and would have had a reasonable expectation of success; and 3) Plaintiffs have not proven any secondary indicia of nonobviousness. As to claim 1, Actavis builds its case for the second proposition, regarding motivation to combine, from the following propositions: 1) MNTX was known to have poor permeability and bioavailability and SLS was known to improve both; and 2) the prior art did not teach away from the use of SLS.

The proposition that all the elements of claim 1 were in the prior art appears to be undisputed. Oral pharmaceutical formulations of MNTX were known in the art,<sup>2</sup> and SLS was known in the art as a pharmaceutical excipient. Neither side contends otherwise.

The terms “permeability” and “bioavailability” have fundamental importance in this case. The relationship between permeability and bioavailability appears to be a complex subject that was sometimes simplified and sometimes blurred in discussions at trial. Dr. Taft presented a demonstrative to help explain “the complicated process of what bioavailability ultimately is.” (Tr. 539:2.) Once a drug is in the GI tract, the first step involves permeating the intestine itself. (Tr. 540:2-3.) Natural barriers in the intestine may prevent that, leading to drug efflux, which prevents drug absorption. (Tr. 540:4-12.) Even if a drug permeates into the intestine, intestinal enzymes may break it down, if the drug is susceptible to drug metabolism. (Tr. 540:13-16.) It is only after passing this series of obstacles that a drug may be absorbed into the bloodstream: “to penetrate into the intestine, to be able to liberate itself from the intestine and avoid intestinal metabolism, now we say it’s in the bloodstream, but that is not bioavailability because we have something called the first pass effect.” (Tr. 540:17-24.) The bloodstream takes the drug to the liver, where it may or may not be metabolized. (Tr. 541:1-7.) To become bioavailable, the drug must escape metabolism in the liver. (Tr. 541:8-14.) Plaintiffs summarized this process

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<sup>2</sup> The parties energetically disputed the issue of whether the closest prior art was an immediate-release oral MNTX formulation, or an enteric-coated oral MNTX formulation, but did not persuade the Court that this distinction makes a material difference. The parties agree that both formulations were known in the prior art. Actavis has failed to demonstrate, by clear and convincing evidence, that it would have been obvious to combine SLS with either one. Perhaps this issue might have eventually become material to the question of whether claim 5, with its immediate release element, was obvious, but the Court found major problems with Defendant’s obviousness case before reaching that point.

as follows: “Oral bioavailability (systemic exposure) is a complicated concept and, modelled mathematically, depends on the fraction of the dose absorbed into the intestine, the fraction of dose absorbed into the intestine that escapes intestinal metabolism, and the fraction of the dose absorbed into the bloodstream that escapes first-pass hepatic metabolism.” (Pls.’ FOF ¶ 122.)

It appeared, however, that the witnesses and the parties used the terms “bioavailability” and “permeability” in ways that suggested varying meanings.<sup>3</sup> As Dr. Taft explained, there is a possible path (really a process), with several obstacles, that may lead from dissolution of orally administered compounds in the GI fluids to systemic availability in the blood plasma. In this opinion, then, for clarity, this Court will define these terms to identify specific points in that process. “Bioavailability” will refer to the endpoint of the process, the extent to which MNTX enters the bloodstream and is available to have an effect wherever blood goes. “Permeability” will refer to the point much closer to the start of the process, the extent to which MNTX, traveling down the GI tract, permeates the lining of the GI tract and is absorbed into the intestine, where it must then face the peril of intestinal metabolism. Permeability and bioavailability are different, and vigilance about the difference is needed in this case.

As to claim 1, the parties strongly dispute whether a POSA would have been motivated to combine MNTX and SLS in a tablet. Actavis begins its argument with the proposition that MNTX was known to have poor permeability and poor bioavailability. At the outset, the Court notes that the choice of adjective here matters: “poor” implies deficiency and a problem to be solved, whereas “low” does not. This has great relevance to the analysis of motivation. From a

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<sup>3</sup> Consider, for example, paragraph 137 in Plaintiffs’ post-trial brief. It is unclear whether “absorption” and “permeation” mean “passage into systemic circulation,” or something else.

semantic perspective alone, “low” value on some dimension is unlikely, without more, to suggest a problem that might motivate a quest for a solution.<sup>5</sup> When a level of something is “poor,” however, one is more likely to view it as a problem which might motivate the search for a solution. If Actavis’ theory contends that a low or lower level of permeability would have motivated the POSA to improve the permeability, the evidence must support the inference that the POSA would have recognized the level of permeability as a problem to be solved.

Plaintiffs provide support for this semantic analysis by pointing to the evidence at trial demonstrating the following proposition: “Drugs with high potency can elicit a pharmacologic response even if they have low permeability—meaning low permeability is not always a problem.” (Pls.’ Br. ¶ 131.) Dr. Taft stated that “the potency of a drug is how much concentration do you need to elicit a certain effect.” (Tr. 565:20-22.) Plaintiffs also point to the definition in the Pandit treatise: “The potency of a drug is the dose needed to produce a certain defined response in an individual.” (P-262.076) Dr. Taft pointed to this teaching of Foss 2001:

N-methylnaltrexone, according to this, has a potency of roughly 30 nanomoles per liter, which means that the concentration that you need at site of action to revert to a block, an opioid receptor, is very low. That means it’s a very potent molecule.

(Tr. 566:11-15, citing Foss 2001, D-40.003.) Dr. Taft also stated that the prior art clinical studies taught that, because MNTX was potent, it was sufficiently permeable to be effective. (Tr. 567:15-17.) Plaintiffs point also to the testimony of Dr. Chambliss, who agreed that “a drug with high potency but poor permeability can still elicit a pharmacologic response . . .” (Tr.

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<sup>5</sup> For example, low body weight may be a goal for some people, but a serious medical problem for others.

240:12-15.) Based on this evidence, the Court finds that low permeability would not, without more, present the POSA with a problem to be solved.

Actavis contends that the experts on both sides agreed that a POSA would have known that MNTX had poor permeability and poor bioavailability. Actavis first cites Dr. Chambliss' testimony that MNTX "was known to have permeability issues." (Tr. 180:2-3.) In support, Dr. Chambliss cited the second paragraph on page 2 of D-74, the Yuan 1997 reference. (Tr. 184:10-185:1.) What this paragraph states, however, does not support Dr. Chambliss' assertion:

Antagonists, such as naloxone, naltrexone and nalmefene, as tertiary compounds, are fairly lipid-soluble and cross the blood-brain barrier easily. Addition of the methyl group at the amine in their ring forms a compound with greater polarity and lower lipid solubility. Therefore methylnaltrexone does not cross the human blood-brain barrier. These properties provide methylnaltrexone with the potential to block undesired side effects of opioid pain medications predominantly mediated by receptors peripherally located (e.g., in the gastrointestinal tract) while sparing opioid effects mediated at receptors in the central nervous system, most importantly the analgesia.

(D-74.002.) This paragraph states that antagonists such as naltrexone are "fairly lipid-soluble" and methylnaltrexone has "lower lipid solubility" relative to antagonists like naltrexone. This does not characterize the lipid solubility in any absolute sense but, instead, simply contends that MNTX is less soluble than compounds that are fairly lipid-soluble.<sup>6</sup> This does not state that MNTX has poor or deficient lipid-solubility, but only that its lipid-solubility is lower than that of

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<sup>6</sup> Similarly, Foss '591 states: "Many quaternary amine opioid antagonist derivatives, such as methylnaltrexone, do not reduce the analgesic effect of opioids. These quaternary amine opioid antagonist derivatives, which have a relatively higher polarity and reduced lipid solubility when compared to the tertiary forms of the drugs, were specifically developed to not traverse the blood-brain barrier or to traverse it at a greatly reduced rate." (P-246.006.) Again, this states only that MNTX has lower lipid solubility when compared to highly lipid-soluble compounds like naltrexone.

naltrexone. Then, the paragraph asserts, without qualification, that these characteristics give MNTX the potential to block undesired side effects in the GI tract. This statement is notable because not only does it not support Dr. Chambliss' assertion of permeability issues but, rather, it may reasonably be read as a statement that Yuan 1997 believed MNTX to have the potential to exert a therapeutic effect on the GI tract without any enhancement of permeability.

Dr. Chambliss then cited a statement on page 7 of Yuan 1997: "As a charged compound, methylnaltrexone's absorption in the gut may be limited, contributing in part to low bioavailability of oral methylnaltrexone." (Tr. 185:2-9; D-74.007.) This statement contains two assertions. The first is that the absorption of MNTX in the gut may be limited, which might conceivably support Actavis' position, but neither Yuan 1997 nor Dr. Chambliss defined "absorption," and there is no basis to conclude that it is a synonym for permeation.<sup>7</sup> The Court notes as well that this part of the sentence says that absorption "may be limited," which suggests that this is uncertain. The next part of the statement asserts low bioavailability, and "bioavailability" here appears to refer to availability in the plasma, since the first sentence of the paragraph states: "Low plasma bioavailability of oral methylnaltrexone has been reported in this study." (D-74.007.) This statement as a whole, thus, supports the proposition that Yuan 1997 taught that oral MNTX has low bioavailability, which is non-controversial and, without more, not evidence about permeability.

Next, Dr. Chambliss cited the finding in Yuan 1997 that a relatively high oral dose of 19.2 mg/kg did not produce high blood levels. (Tr. 185:14-25.) Dr. Chambliss finished his

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<sup>7</sup> As suggested earlier, "absorption" was another word that, both during the trial and in the prior art, appeared to be used to mean a number of different things.

discussion of Yuan 1997 with this statement of what the POSA would understand that Yuan 1997 taught with regard to the permeability of MNTX: “That methylnaltrexone has poor permeability for developing an oral formulation. You need to address that.” (Tr. 186:3-7.) The Court finds that Dr. Chambliss’ opinion about the teachings of Yuan 1997 is not supported by the text of that reference. Actavis has pointed to nothing in Yuan 1997 that teaches that there was a problem with the permeation of MNTX into the opioid receptors in the GI tract.<sup>8</sup> Nor do the cited portions of Yuan 1997 support the proposition that the prior art believed that low bioavailability was a problem to be solved. To the contrary, Yuan 1997 taught, as Plaintiffs contend, that MNTX worked just fine for that purpose. This Court finds that Dr. Chambliss’ testimony that MNTX was known in the prior art to have “permeability issues” is unsupported by the evidence of record and will not be accorded weight.

Next, Actavis cites this testimony from the cross-examination of Dr. Williams:

Q. You agree that a person of ordinary skill in the art would understand that methylnaltrexone had poor permeability. Is that right?

A. Yes.

(Tr. 484:14-17.) This quote appears to say exactly what Actavis contends it says, but the Court makes several observations. First, the question was asked without any clear qualification as to the time frame. There is no way to know whether Dr. Williams’ answer addressed the understanding of the POSA before the critical date or after. Second, Dr. Williams was not asked to articulate the basis for his statement. Third, because there was no development of this point,

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<sup>8</sup> Yuan 1997 states that MNTX has “lower lipid solubility” than “fairly lipid soluble” compounds like naltrexone. (D-74.002.) In its post-trial brief, Actavis asserts that a POSA would understand this to mean that MNTX has poor permeability. (D.’s FOF ¶ 123.) But that is plainly not what Yuan 1997 says, and this is representative of the inferential leaps that Actavis takes in making the case that the prior art recognized the permeability of MNTX as poor.

it is not clear what Dr. Williams meant by “poor.” Cross-examination of Dr. Williams did not elicit any clear statement that the prior art understood that the permeability of MNTX was poor to the extent that it was an obstacle to effectiveness and needed remediation. Moreover, the Court considers this testimony together with the rest of Dr. Williams’ testimony. On direct examination, Dr. Williams stated clearly that he disagreed with Dr. Chambliss that a person of ordinary skill in the art would have been motivated to improve the absorption and bioavailability of oral formulations of MNTX. (Tr. 452:9-15.) Dr. Williams then stated that, for a POSA, “the goal would not be to improve absorption and bioavailability” of MNTX. (Tr. 452:20-23.) Given those very clear statements, the Court does not find this unclear statement to deserve any weight.

Next, Actavis cites this testimony from the cross-examination of Dr. Taft:

Q. Okay. So a person of ordinary skill in the art would know both that it's a low permeability drug and that it's a low bioavailability drug, right?  
A. Yes, that's fair.

(Tr. 645:24-646:2.) Dr. Taft did not agree that MNTX was known to have poor permeability, but that it had low permeability. As already discussed, low permeability does not imply a problematic characteristic in need of remedy. Dr. Taft, in fact, stated this clearly on direct examination:

Q. Let's take a step back. Did you hear Dr. Chambliss testify that a person of ordinary skill in the art would have wanted to use a permeation enhancer or ion pairing agent generally with methylnaltrexone?  
A. Yes.  
Q. Did you agree with that opinion?  
A. No, I did not.  
Q. Why not?  
A. Well, first of all, the prior art did not indicate that bioavailability or permeation was a problem for oral methylnaltrexone.

(Tr. 585:7-18.) Dr. Taft clearly stated that the prior art did not indicate that permeation was a problem for oral MNTX. Dr. Taft's testimony does not support the proposition that the prior art believed that MNTX had poor permeability such that it was a problem to be solved.

Next, Actavis points to Dr. Chambliss' opinion that MNTX was known to have a positive charge, and that, generally, drugs with a positive charge have poor permeability. (Tr. 183:7-20.) Dr. Chambliss did not state, nor was he asked, whether or not the prior art understood MNTX as conforming to this general rule. It was directly after Dr. Chambliss stated this that counsel asked him whether there were any references in the prior art that discuss the poor permeability, and this led to his testimony about Yuan 1997, as just discussed. (Tr. 183:21-25.) As already discussed, this Court finds that Yuan 1997 does not support Dr. Chambliss' permeability opinions.

Next, Actavis points to the specification and the Accordingly Phrase, contending:

[T]he Background of the Invention section of the '276 patent is consistent with Dr. Chambliss's testimony that the prior art taught that an oral formulation of MNTX with improved permeability and bioavailability was needed. Supra ¶¶ 36-39. After describing results of prior art studies with oral formulations of MNTX, and identifying the shortcomings of those studies, the inventors conclude that “[a]ccordingly, the need exists for bioavailable oral dosage formulations comprising methylnaltrexone.” P-1.011 at 2:61-62; Tr. 186:16-187:13 (Chambliss).

(Defs.' FOF ¶ 125.) This is unpersuasive, as Actavis has failed to explain what in the specification is consistent with Dr. Chambliss' testimony. The “Background of the Invention” section of the specification does not use the words “permeability” or “permeation.” Later in the specification, when describing certain embodiments, the patent states: “The amphiphilic [sic] pharmaceutically acceptable excipient increases the lipophilicity of the composition thereby allowing for increased transport through the unstirred diffusion layer in the GI tract, resulting in

increased permeation through biological membranes.” ’276 patent, col.13 ll.58-63. This demonstrates that the patentees knew how to specify permeation through membranes when they chose to do so, and they did not choose to do so in presenting the Background of the Invention. The descriptions of the prior art patents in that subsection make no reference to concepts of permeability, or even bioavailability, with the exception of the Accordingly Phrase.

At trial, the parties debated the meaning and significance of the Accordingly Phrase. The bottom line issue concerns what is essentially an attempt by Actavis to rewrite the sentence by inserting the word “more” before “bioavailable.” The Court makes a few observations about the phrase, which is the terminal sentence in the Background of the Invention subsection. First, its antecedent foundation is unclear at best. As stated, there is no reference in the subsection, outside of the Accordingly Phrase, to bioavailability. The closest it comes is in the description of the ’158 patent, with a reference only to average peak plasma levels. ’276 patent, col.2 ll.15-17.

Second, given the lack of antecedent reference to bioavailability, the meaning of the word “bioavailable” in the Accordingly Phrase is unclear, and so this Court considers the context to understand its meaning. The Background of the Invention subsection starts by describing the use of opioids for the treatment of pain, and the side effect of constipation, “which can be debilitating and often cause patients to refuse the use of opioid analgesics.” ’276 patent, col.1 ll.27-29. The subsection then discusses the problem this can cause in the treatment of post-surgical pain. Next, it points to the problem of opioid receptor antagonists that cross the blood-brain barrier, and then turns to MNTX. It then surveys the prior art use of MNTX as a treatment for OIC.

The Court finds no antecedent to illuminate the meaning of the Accordingly Phrase and concludes that it is too ambiguous to be read as a significant statement about anything. Given the context, the Background of the Invention subsection, and the lack of clarity about its meaning, the Court can only conclude that the Accordingly Phrase indicates the general view of the inventors that the prior art demonstrated a need for a more effective oral MNTX formulation. The Court thus understands the Accordingly Phrase to be an unremarkable transitional statement, and not more. There is no basis to consider this to be a detailed statement of specific teachings of the prior art.

Because the Accordingly Phrase is not a specific statement about the teachings of the prior art, the Court need not strain to interpret the meaning of “bioavailable.” There is nothing in the Background of the Invention subsection that supports Actavis’ attempt to rewrite “bioavailable” as “more bioavailable.” Actavis has not pointed to any language in the subsection that would justify such an interpretation.

Nor does this Court agree with Actavis that the Accordingly Phrase constitutes a binding admission regarding the prior art, within the meaning of Pharmastem Therapeutics, Inc. v. Viacell, Inc., 491 F.3d 1342, 1362 (Fed. Cir. 2007) (“Admissions in the specification regarding the prior art are binding on the patentee for purposes of a later inquiry into obviousness.”) The Court has found the Accordingly Phrase to be an unremarkable transitional statement, not an admission about the prior art.

The interpretation of the Accordingly Phrase is a key building block in Actavis’ obviousness case, and the Court’s determination that it does not mean what Actavis proposes leaves Actavis with a major hole in its case.

Next, Actavis quotes the testimony of one of the inventors, Dr. Al-Shareffi, contending that it corroborates that a POSA would have wanted to improve the bioavailability of MNTX. This is problematic for several reasons. First, an inventor's insights are not part of the prior art. Second, in the quoted testimony, Dr. Al-Shareffi made a general observation that all formulators want to make a formulation that has better bioavailability. This is not a statement about MNTX, or about the prior art; it is a statement about the general motivations of formulators. Third, as Dr. Taft opined in his testimony, and as will be discussed in detail below, the prior art taught that plasma levels should be kept low to avoid side effects like orthostatic hypertension, and the invention claimed in the '276 patent did not increase bioavailability. For all these reasons, the Court concludes that Dr. Al-Shareffi's statements do not, as Actavis argues, corroborate or support the proposition that a POSA would have wanted to improve the bioavailability of MNTX.

Plaintiffs contend that there was no motivation to increase the permeability of MNTX in the prior art. Dr. Williams testified that he did not agree with Dr. Chambliss that a POSA would have been motivated to improve the absorption and bioavailability of oral formulations of methylnaltrexone. (Tr. 452:9-15.) As already discussed, Dr. Taft stated that prior art clinical studies taught that, because MNTX was potent, it was sufficiently permeable to be effective. (Tr. 566:11-567:17.)

Plaintiffs next contend that the prior art recognized that, when orally administered drugs have a local site of action:

approaches were sought to limit systemic exposure because systemic drug levels can lead to side effects. . . For example, Foss '591 (P-246) explains that achieving efficacy with low or no systemic levels is desirable, for example, because it greatly reduces the potential risk of adverse side effects. (P-246.006 at

2:61-64 (Foss '591); P-246.009 at 7:47-62 (Foss '591).)

(Pls.' Br. ¶ 136.) Dr. Taft testified that the prior art taught that “it was preferred to keep the systemic levels, the plasma levels, low because of the known side effects or expected side effects of methylnaltrexone systemically, including orthostatic hypertension.” (Tr. 556:17-557:3.) Dr. Rauck agreed that “elevated . . . plasma levels of methylnaltrexone, can produce orthostatic hypotension.” (Tr. 382:11-21.)

Plaintiffs then argue:

Where absorption into the bloodstream and systemic exposure are unnecessary and potentially result in side effects, increasing permeation at all would be particularly undesirable. A person of ordinary skill in the art, far from wanting to increase methylnaltrexone’s absorption, would in fact seek to *minimize* its absorption and thus its systemic levels.

(Pls.' Br. ¶ 137.) In support, Plaintiffs cite to a number of pieces of evidence, but the evidence supports this argument only in part. It is undisputed that oral MNTX acts locally, not systemically, to relieve OIC, and it is clear that MNTX in the plasma can cause undesirable side effects. Moss 2008 states:

After oral administration, extremely low plasma concentrations are observed; enteric coating reduces the concentrations further, suggesting that a small amount of the drug may be absorbed in the upper gastrointestinal tract. No correlation exists between drug effect and plasma concentrations after doses of 3.2 mg/kg or 6.4 mg/kg of enteric-coated MNTX.

(P-258.003.) In support, Moss cites the Yuan 2000 Enteric study. The Yuan 2000 Enteric study states that the tested enteric formulation was designed “to achieve lower plasma levels of the compound.” (P-275.002.) In discussing the results, the Yuan 2000 Enteric study stated: “results from this study showed that administration of enteric-coated methylnaltrexone prevents gastric absorption of the compound, resulting in lower plasma levels.” (P-275.006.) Moss

2008 and Yuan 2000 Enteric support the proposition that the prior art believed that low plasma concentrations of MNTX were desirable.

Furthermore, the passage from Moss 2008 just quoted teaches that “[n]o correlation exists between drug effect and plasma concentrations after doses of 3.2 mg/kg or 6.4 mg/kg of enteric-coated MNTX.” Dr. Taft confirmed that this means what it says: plasma levels do not correlate with drug effects. (Tr. 560:6-12.) Yuan 2000 RL taught that, at three dosage levels at 3.0 mg/kg and below, low plasma levels indicated that MNTX acted directly in the GI tract. (D-374.007.) Since Moss 2008 taught that increasing plasma concentration with doses above 3.2 mg/kg does not affect drug effect, the two references together teach that there is no significant relationship between plasma level and drug effect, and thus that increasing plasma level of MNTX does not increase the drug effect. Similarly, Foss 2001 found “no correlation between changes in transit time and the MNTX plasma concentrations over a 3-hour period.” (D-40.004.) The prior art of record does not teach that oral MNTX formulations with improved bioavailability were needed in order to improve treatment efficacy, and Actavis has not pointed to any prior art reference that teaches otherwise.

Actavis contends that Yuan 2000 RL taught that increases in plasma levels were associated with increases in efficacy (decreased time to laxation), and thus that time to laxation decreases as bioavailability increases. In support, Actavis cites the testimony of Dr. Taft: “Dr. Taft agreed that data from the Yuan 2000 Research Letter shows that as the bioavailability of MNTX increases, the average time to laxation decreases.” (D’s FOF ¶ 171.) This statement is not supported by the record:

Q. Okay. So let's move onto the one milligram per kilogram dose, okay. The mean time to laxation went down from 18 to 12.3. You agree with me on that?

A. Yes, that's what it says in the table, yes.

Q. Okay. And one patient in that group did have detectable plasma levels, right?

A. Yes. It would be whatever was above the minimum level that you can detect from the analytical instrument.

Q. Okay. So the time to laxation went down, and the bioavailability went up in this study with this group, correct?

A. I don't agree with that, no.

Q. All right. Let's move on then. Three milligrams per kilogram, mean time to laxation went down, again, right, to 5.2 hours?

A. Yes.

Q. And the plasma levels this time were detected in three of four patients, right?

A. That's correct, yes.

Q. Okay. So, again, the plasma -- the peak plasma levels are going up and the mean time to laxation is going down. Do you see that? Just numerically, do you see that on the chart?

A. I see that numerically, yes.

(Tr. 613:3-614:2.) The cross-examination refers to a demonstrative exhibit which Actavis had created, based on Yuan 2000 RL. The exhibit shows, correctly, that plasma levels of MNTX were undetectable in the four patients in lowest dosage group, detectable in one of four patients in the middle dosage group, and detectable in three of four patients in the highest dosage group.

(D's. Post-Trial Br. 63.) Contrary to Actavis' argument, the transcript shows that Dr. Taft expressly disagreed with the conclusion that Actavis now contends he agreed with. Furthermore, Yuan 2000 RL, in discussing the results, absolutely did not find that increases in bioavailability are associated with decreased time to laxation. (D-374.007.) To the contrary, the concluding paragraph states: "The low methylnaltrexone plasma levels observed in our study suggest that this charged compound acts directly in the gut." (*Id.*) This is opposite to what Actavis would have this Court believe about what the study found. Actavis has shown no basis to find that either Yuan 2000 RL or Dr. Taft's testimony about it supports its bioavailability

argument.<sup>10</sup>

The evidence clearly supports the inference that the POSA, when creating an orally administered MNTX formulation at the critical date, would have sought to minimize plasma levels of MNTX. The evidence does not establish, however, a key step in Plaintiffs' argument: the proposition that the POSA would have therefore believed that increasing permeation was undesirable. The evidence clearly shows that the POSA would have believed that increasing plasma levels was undesirable, but it does not show what effect this belief had on beliefs about increasing permeation. Dr. Taft stated that Clinical Study 3200A3-115 demonstrated that the invention of the '276 patent, an SLS formulation, did not show different bioavailability than the same formulation without SLS. (Tr. 576:1-9.) Dr. Taft also stated that the 1115 Study showed that the inventors' formulation was effective, but not due to increased bioavailability. (Tr. 575:22-24; 633:20-22.) This suggests that permeation may, in fact, be increased without a concomitant increase in bioavailability.

In its responsive brief, Actavis appears to raise a common-sense proposition: it is better to use less of a drug than more, and cites Aungst 1993 in support. Indeed, Aungst 1993 states that low bioavailability leads to waste:

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<sup>10</sup> The Court comments that neither party has focused on the implications of the results reported in Yuan 2000 RL. Consider the POSA studying those results. It is easy to imagine a POSA viewing the result of an average of roughly 5 hours to laxation in the 3.0 mg/kg dosage group, and wanting to improve upon the formulation to make it work faster. What improvement would have been obvious? Actavis picks out permeation enhancement, but does not point to anything in Yuan 2000 RL which might suggest this approach. Actavis does not mention what might be obvious from Yuan 2000 RL: because the results demonstrated that increasing the dosage decreased the time to laxation, it might be obvious to increase the dosage more, to see if this further decreases time to laxation. Why is that not the most obvious approach to improving the Yuan 2000 RL oral formulations? The fact that Actavis does not even mention this possibility is consistent with the operation of hindsight.

For drugs that are expensive to produce, wasting 80% of the material may not be acceptable. Maximizing bioavailability contributes to increasing cost-effectiveness.

(D-36.001.) Actavis has neither argued nor presented evidence that MNTX is expensive to produce. This Court has no basis to infer that cost-effectiveness would have motivated a POSA in designing an MNTX oral formulation. Instead, the Court has significant evidence that the likelihood of increased serious side effects would have motivated a POSA to not increase the bioavailability of MNTX. This record does not support any other inference.

In the responsive brief, Actavis argues that Plaintiffs have offered no evidence of concern about the side effect of orthostatic hypertension. This is incorrect. In addition to the expert testimony on this subject already discussed, Foss '591 states:

As with most drugs, it is desirable to maintain the lowest possible systemic levels of MNTX which are sufficient to provide the desired therapeutic effect. For example, elevated circulating levels of MNTX can result in orthostatic hypotension. The present discovery provides an unexpected means to avoid such undesirable drug side effects by lowering the dose administered and subsequently minimizing circulating levels of the drug. Since endogenous and externally supplied opioid-induced inhibition of gastrointestinal motility and constipation is thought to result from opioid receptors located within the gastrointestinal tract, enterically coated MNTX or other QDNMs may provide a local administration of the drug that does not require a circulating level for effective prevention or treatment of symptoms. Thus, the amount and/or frequency of drug administered can be reduced.

'591 patent, col.7 ll.47-62. The Court finds that the prior art recognized the need to minimize systemic levels of MNTX to minimize side effects like orthostatic hypotension.

Actavis contends that the art, as of the critical date, taught that oral formulations of MNTX did not achieve an adequate time to laxation, citing this statement in Moss 2008: "Methylnaltrexone has also been developed in a subcutaneous formulation designed to avoid the long delay associated with oral dosing." (P-258.004.) This statement appears right after a

discussion of Yuan 2000 RL which, at the highest oral dose, reported a mean time to laxation of about 5 hours. (D-374.006.) This evidence supports the inference that the prior art, as of the critical date, recognized a need to find a treatment that worked faster, and this appears likely to be a correct statement. It does not support any inference about how to achieve the goal of faster constipation relief. Actavis has shown that the prior art recognized a need for treatments providing faster constipation relief, and that existing oral formulations were not fast enough, but not more.

The Court's uncertainty about what the prior art understood about whether permeation could be increased without a concomitant increase in bioavailability does not weaken Plaintiffs' argument that there was no motivation to increase the permeability of MNTX in the prior art. Having considered the parties' arguments and the evidence of record, the Court finds that Actavis has only the unsupported and conclusory opinions of Dr. Chambliss to support its contention that a POSA, prior to the critical date, would have had the motivation to find an oral formulation of MNTX that improved permeability. Dr. Chambliss stated that he based his opinion on Yuan 1997, but, as discussed, not only does Yuan 1997 not support the assertions Dr. Chambliss made about it, its findings differed markedly from Dr. Chambliss' statements about it. The Court concludes that, on this subject, Dr. Chambliss has low credibility, and his testimony is given little weight both because of his low credibility and the lack of evidentiary support. The other evidence cited by Actavis is even weaker. Significantly, Actavis has not pointed to any piece of prior art that states what Actavis argues was well-known.<sup>11</sup> The very weak evidence of

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<sup>11</sup> As already discussed, the prior art of record taught only that MNTX had lower lipid solubility than highly lipid-soluble compounds like naltrexone.

record does not suffice to establish, even by a preponderance of the evidence, that the prior art recognized that the permeability of MNTX needed improvement, or that an oral formulation of MNTX with improved permeability was needed. As such, Actavis has failed to prove this point by clear and convincing evidence. This factual determination has a decisive impact on Actavis' obviousness case. This proposition provided the foundation for it. Without this foundation to provide a motivation to combine the prior art references, Actavis cannot prove that claim 1 is invalid for obviousness, nor that claims 2 or 5 are obvious.

Even if Actavis had proven that a POSA would have been motivated to improve the permeability of MNTX to improve the efficacy of oral formulations, Actavis would still fail to show that it would have been obvious to combine MNTX and SLS in a tablet. The prior art cited by Actavis disclosed a wide array of options for a POSA faced with the purported permeability problem, with no reason to pick out SLS, which appears to be just one whitecap in a sea of choices.

Given the absence of evidence to support the inference that the prior art recognized a problem of poor permeability in oral MNTX formulations, there is a strong risk that Actavis' theory relies on hindsight. A case with important similarities is Mintz v. Dietz & Watson, Inc., 679 F.3d 1372, 1377-78 (Fed. Cir. 2012), in which the Federal Circuit held:

This statement of the problem represents a form of prohibited reliance on hindsight. The district court has used the invention to define the problem that the invention solves. Often the inventive contribution lies in defining the problem in a new revelatory way. In other words, when someone is presented with the identical problem and told to make the patented invention, it often becomes virtually certain that the artisan will succeed in making the invention. Instead, PCM must prove by clear and convincing evidence that a person of ordinary skill in the meat encasement arts at the time of the invention would have recognized the adherence problem recognized by the inventors and found it obvious to produce the meat encasement structure disclosed in the '148 patent to solve that problem.

(Id.) Here, there is reason to suspect that Actavis' statement of the problem to be solved relies on hindsight. The evidence of record in this case does not establish that the prior art POSA would have recognized an oral MNTX permeability problem, and would have been motivated to improve permeability as the inventors did. See also In re Kahn, 441 F.3d 977, 988 (Fed. Cir. 2006) (“In considering motivation in the obviousness analysis, the problem examined is not the specific problem solved by the invention”); Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH, 139 F.3d 877, 881 (Fed. Cir. 1998) (“Defining the problem in terms of its solution reveals improper hindsight in the selection of the prior art relevant to obviousness.”)

## **2. The selection of SLS**

The next key proposition for Actavis' obviousness argument is that a POSA, having recognized that MNTX had poor permeability in oral formulations, would have selected SLS to improve the permeability of MNTX. Given the factual finding that the prior art did not recognize the permeability of MNTX as a problem to be solved, nor as a characteristic in need of improvement, this proposition cannot be proven: if there is no motivation to look for a permeation enhancer, it cannot be obvious to select a particular permeation enhancer to combine with MNTX. Nonetheless, for the sake of completeness, the Court will consider Actavis' argument in support of this proposition. The Court finds significant problems in addition to the lack of foundation.

The missing foundation is the proposition that the prior art recognized the poor permeability of MNTX as a problem to be solved by improving permeability. Even if the Court had decided that factual issue in favor of Actavis, however, there are big gaps in the road that Actavis contends leads to the selection of SLS. Actavis' next step on that road is to cite Dr.

Chambliss' testimony about Table 1 in Aungst 1993. Table 1 is titled, "Categories of Oral Bioavailability Problems, Methods to Identify those Problems, and Formulation Approaches." (D-36.002.) Actavis does not explain why a POSA, faced with the challenge of improving the permeability of MNTX, would have looked to Table 1. As already established, the prior art did not believe that there was any problem with the bioavailability of MNTX. Moreover, the prior art taught that increasing bioavailability increased the risk of side effects such as orthostatic hypotension. Actavis' use of Table 1 is hindsight-driven: the predicate appears to be that the POSA would disregard the fact that Aungst 1993 primarily addresses bioavailability problems and that the title of Table 1 expressly states that it concerns bioavailability problems, but look there nonetheless to address a permeation problem because one of the listed problems is "poor membrane permeation." (Id.) The text directly above Table 1 states: "Based on the processes depicted in Scheme I, one can categorize the most common causes of poor oral bioavailability. These categories and sub-categories are listed in the first column of Table 1." (Id.) Given that this Court has determined that the prior art did not believe MNTX had poor oral bioavailability, why would a POSA have even looked at Table 1 in Aungst 1993 to help solve the purported permeation problem?<sup>12</sup>

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<sup>12</sup> Moreover, Actavis points to Table 1 but overlooks what Aungst 1993 states in the discussion of Table 1, as Dr. Taft pointed out in his testimony (Tr. 591:1-15), and Dr. Chambliss acknowledged in his (Tr. 256:4-21.) In the discussion of Table 1, Aungst 1993 states: "Another approach is to modify the drug structure to increase lipophilicity, reduce molecular weight, or replace hydrogen bonding groups. In many instances, the design of membrane permeation properties into an active compound may be more likely to succeed in improving permeation than formulation approaches." (D-36.003.) Thus, in the text, Aungst points to some additional possible ways to improve permeation and suggests that incorporation of the permeation enhancer into the active compound is more likely to succeed. This is not the approach the inventors took in claims 2 and 5. Rather, with these statements, Aungst 1993 taught away from the inventive formulation.

Why, in fact, would a POSA seeking to improve oral MNTX formulations have looked at Aungst 1993 at all? Consider the first sentence of Aungst 1993: “Bioavailability is the fraction or percentage of a dose that reaches the systemic circulation intact, when not directly injected into the circulation.” (D-36.001.) As established, the prior art did not seek to increase the amount of MNTX that reaches systemic circulation. A reference teaching ways to increase how much drug reaches systemic circulation would not have been relevant to a POSA seeking to improve an oral MNTX formulation. Actavis’ use of Aungst 1993 appears to be hindsight-driven cherry-picking.

Moreover, those problems aside, even if the POSA found a way to Aungst 1993 and to the section of Table 1 that Actavis has picked out, Table 1 lists 3 subcategories of permeation problems: “poor partitioning,” “low diffusivity,” and “binding to mucus or membrane.” (Id.) If there is any evidence of record that demonstrates that the prior art understood any of these to apply to MNTX, Actavis has not cited it. Presumably, a POSA would check to see if the presumed permeability problem with MNTX fit into any of these subcategories, before looking at the suggested solutions.

According to the Actavis theory, which skips over the subcategories, the POSA then looks at the “Possible Solutions” column in Table 1 which, for the “Poor membrane permeation” category, lists these solutions: “permeation enhancers,” “ion pairing,” “complexation,” and “lipid or surfactant vehicles.” (Id.) Table 1 thus appears to present five options for solutions to the problem. How does the POSA decide which one to choose? Actavis does not say, but selects permeation enhancers as if the other possibilities need not be dealt with. Actavis cites Dr. Chambliss’ testimony on this point, and Dr. Chambliss lists all five solutions listed in Table 1,

and then states:

Q. Now, what would a person of ordinary skill in the art understand from the teachings of Aungst 1993 with regard to improving the permeability of an oral methylnaltrexone product?

A. Well, they would know that the typical solution would be to use a permeation enhancer, perhaps try ion pairing or use a surfactant vehicle.

(Tr. 190:11-17.) Here, Dr. Chambliss discards without explanation two of the solutions, complexation and lipid vehicle, and selects three for consideration. Dr. Chambliss then jumps the logical gap to selecting the permeation enhancer option. Neither Actavis nor Dr. Chambliss explain why this is the obvious choice from the five options. Actavis acknowledges that Table I states a number of solutions to the problem of poor permeability, and quotes Dr. Williams in support of the idea that the POSA would likely have worked on “several formulation strategies simultaneously,” one being the use of permeation enhancers. (D’s FOF ¶ 130; Tr. 484:18-25.) The next step on the path to SLS is unclear from Defendant’s post-trial brief. Defendant jumps ahead to what the POSA would know about SLS and MNTX. But there is a big gap here: Actavis proposed that the POSA would work on several formulation strategies simultaneously. Actavis does not clearly articulate the path to the selection of SLS as the obvious choice.

Actavis next points to the evidence that SLS was known in the prior art both as a pharmaceutical excipient and as a permeation enhancer. This is undisputed; Table II in Whitehead 2007 lists SLS as the fifth most safe and effective permeation enhancer of the 51 reviewed. (D-49.004.) Actavis has one paragraph in its brief, number 138, that appears to be intended to bridge the gap, stating a set of criteria that the POSA would have used to find a permeation enhancer (still leaving unexplained why permeation enhancers would have been the obvious choice, given the group of options in Table 1 and the other teachings of Aungst 1993).

The key question is: out of the universe of permeation enhancers<sup>13</sup> – and Actavis does not contend that the options here are few – why would the POSA view SLS as the obvious choice? Actavis contends that the POSA would have five criteria to use to select a permeation enhancer, which it summarizes as follows:

In sum, SLS was the obvious choice for a POSA to improve the permeability for MNTX because it satisfied all the criteria a POSA would use to select an excipient for that purpose:

- SLS was known to be safe and effective, and was reported by Whitehead 2007 to be the safest and most effective anionic surfactant in the list of 51 permeation enhancers studied.
- SLS was widely used as an anionic surfactant.
- SLS had the potential for ion pairing.
- SLS had been widely used in oral pharmaceutical formulations.
- SLS was reported to be compatible with MNTX.

(Def.'s Br. ¶ 138.) These criteria are roughly similar to those stated by Dr. Chambliss: 1) an excipient that is a permeation enhancer; 2) anionic surfactant; 3) has the potential for ion pairing; 4) safe and effective for use in oral formulations; 5) compatible with MNTX. (Tr. 190:18-191:5.

Dr. Chambliss listed these criteria, and then stated:

Q. And now based on those considerations, is there any particular excipient that a person of ordinary skill in the art would have used for methylnaltrexone, Dr. Chambliss?

A. I believe sodium lauryl sulfate would have come to top of mind.

Q. Why is that?

A. It meets all of these categories.

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<sup>13</sup> The van Hoogdalem reference is useful evidence of the magnitude of the universe of prior art permeation enhancers for use in improving intestinal drug absorption. (P-272.) As Dr. Williams stated (Tr. 462:11-24), Table I in van Hoogdalem lists eighteen *categories* of enhancers. (P-272.006.) Many of the categories list multiple examples. The Aungst 2000 review article surveyed eight categories of intestinal permeation enhancers. (D-65.004-.010.) Neither reference singles out SLS as a preferred option.

(Tr. 191:6-12.)

Actavis' post-trial brief does not refer to Dr. Chambliss' "top of mind" principle but, as quoted above, simply says that SLS was the obvious choice because it satisfied all the criteria.<sup>14</sup> (Def.'s Br. ¶ 138.) The set of criteria (hereinafter, the "Chambliss List") appears to be a kind of gap-filling mortar for the theory. It has a very large gap to fill. The idea appears to be that the POSA would have a set of criteria that would be used to select the permeation enhancer to use with MNTX, and that application of those criteria leads to SLS, making SLS obvious.

The Chambliss List is akin to a magic black box: you put in diverse teachings of the prior art, and it gives you SLS. Defendant's use of the Chambliss List is very problematic, and it attempts to cover over a big gap in the obviousness theory. First, consider the last step, selection of SLS. Actavis contends that the application of these factors leads to SLS, but this depends at least on establishing the factual predicate that, given those criteria, there was only one compound that fit them. Actavis did not establish this predicate. The record contains no evidence about how many compounds would have fit the criteria in the Chambliss List. Actavis has pointed to no evidence that supports the inference that SLS is the only one.

Second, Actavis skips over the creation and assembly of the Chambliss List itself. This is especially problematic because the Chambliss List – at work inside the black box – does the work of selecting and combining the various prior art elements, but away from scrutiny. Crucially, neither Dr. Chambliss nor Actavis have made any case that it would have been obvious for the prior art POSA to combine the prior art to assemble this schema of the five

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<sup>14</sup> Actavis, in its responsive brief, states: "SLS would have been at the top of a short list." (D.'s Resp. Br. 10.) Conspicuously absent from Actavis' case are the other entries on that list, and an explanation of why SLS would have been not merely the top choice, but the obvious choice.

criteria. What is the evidence that the POSA, prior to the critical date, would have put together this list of criteria? It is not enough to show that each one of these, individually, is a teaching or a sensible inference from the prior art – not that Actavis has shown even that. The Chambliss List itself is a combination of prior art teachings, unsupported by any analysis.

If the Court accepted this approach, it would be allowing an end run around the center of the obviousness inquiry. The obviousness inquiry here focuses on the motivation to combine the pieces of prior art. Actavis here attempts to use both expert testimony and sleight of hand to circumvent this requirement. Dr. Chambliss simply selects and combines various teachings drawn from the prior art and presents the patchwork as if it were itself a piece of prior art. Actavis then presents Dr. Chambliss' patchwork and avoids the burden of showing how and why a POSA would have selected and combined the elements to create the scheme.<sup>15</sup> If this approach was allowed to succeed, every patent would be invalidated as obvious based on the conclusory testimony of an expert that it was obvious to combine the elements found in the prior art. The law requires more. In the absence of any evidence demonstrating that this list of criteria is itself in the prior art, the risk is high that it is a hindsight-driven attempt to escape the obligation to show the motivation to select and combine its components.<sup>16</sup>

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<sup>15</sup> Just as one of many possible examples, consider two of the criteria, permeation enhancer and ion pairing. As Table 1 of Aungst 1993 states, and as Dr. Chambliss affirmed (Tr. 189:14-24), permeation enhancers and ion pairing are two of five possible solutions for poor permeability. Actavis, in constructing this list of criteria, has turned two alternate solutions into one solution with both characteristics. This is combining pieces of prior art, but it is done surreptitiously, and so it would be important to ask Actavis to prove that it would have been obvious to combine permeation enhancers with ion pairing as a solution to permeability problems. As another example, how did anionic surfactant get on this list? Neither Dr. Chambliss nor Actavis has established that the genus of anionic surfactants is the obvious choice.

<sup>16</sup> In particular, the inclusion of “ion pairing” on that list of criteria is a red flag that hindsight is at work and that this is indeed an attempt at an end run. Given claim 2, there is no getting

In short, Actavis has failed to demonstrate that, even if the foundation proposition had been proven, it would have been obvious to a POSA to select SLS as the solution to the problem. Actavis has failed to propose a complete theory to explain how a POSA looking at Table 1 of Aungst 1993 would have selected SLS as the obvious choice.

Actavis also points to WO '352 as a prior art reference that teaches the use of SLS as an excipient with MNTX. This is correct but incomplete: WO '352 teaches the use of SLS as an excipient with MNTX, but as a lubricant, and not as anything else, such as a permeation enhancer. (D-73.023.) Actavis has not explained how use as a lubricant might have played any role in the selection of SLS as a permeation enhancer.

The Court finds that, even if the prior art had recognized that MNTX had poor permeability in oral formulations, Actavis has failed to show, by clear and convincing evidence, that the choice of SLS as the solution to those problems would have been obvious to a POSA.

### **3. Teaching away**

Plaintiffs argue that the prior art taught away from using SLS with a quaternary ammonium compound like MNTX. The parties agree that MNTX belongs to a genus of chemical compounds termed “quaternary ammonium compounds” (“QAC.”) Plaintiffs contend that prior art studies showed that SLS failed at increasing absorption of QACs, and point to the Kakemi and Langguth references. Dr. Chambliss agreed that a POSA creating an oral MNTX formulation would look to other QACs. (Tr. 237:7-10.)

Kakemi is a 1969 journal article reporting on a research study which investigated, *inter*

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around the necessity of showing why an ion-pairing solution was the obvious one, and Actavis has not shown that.

*alia*, the effect of SLS on rectal absorption of poorly absorbable compounds, including three QACs. (P-253.001, P-253.005.) Kakemi reported: “no absorption of strong quaternary ammonium compounds could be detected.” (P-253.004.)

Langguth is a 1987 journal article reporting on a research study which investigated, *inter alia*, the effect of various counterions, including n-alkyl sulfates, on the permeation of the quaternary ammonium compound trospium across rat intestine and human abdominal epidermis. (P-254.004.) Langguth reported these results:

From our investigations it can be seen that permeation through membranes as a function of counter ion chain length more or less resembles a Gauss' distribution curve with maximum permeation in the range of medium chain length of the counter ion (n=7, n=9). Below and above this range permeation drops to levels that are only slightly different than the original compound.

(P-254.006-007.) The parties do not dispute that SLS has a chain length of 12. Langguth thus teaches that n-alkyl sulfates like SLS, which has a chain length of 12, are associated with only slightly increased permeation of the QAC trospium, and that it is n-alkyl sulfates with a chain length of 7 or 9 that maximally increase permeation.

Plaintiffs also point to the statements of the examiner in the Notice of Allowability during prosecution of the '276 patent. What follows is the “Reasons for allowance” section in its entirety:

The following is a statement of reasons for the indication of allowable subject matter: As evidenced by Langguth et al. . . ., a way to increase the lipophilicity of hydrophilic quaternary compounds “is by formation of corresponding ion pairs with longchain counterions of opposite charge.” Page 1362. However, Langguth et al. also notes that “[o]n the other hand there are also investigation where no significant enhancement of ion pair absorption across intestinal wall was concluded.” Accordingly, it is not certain in view of the prior of record that a pharmaceutical composition comprising methylnaltrexone cation and dodecyl sulfate anion, particularly in the amount claimed, would have been obvious to one of ordinary skill in the art and had a reasonable expectation of success.

(P-11.731.) The examiner thus made clear that the decision relied significantly on the teachings of Langguth.

Plaintiffs also point out, correctly, that Actavis has misinterpreted the meaning of Table IV in Aungst 1993. As previously stated, Aungst 1993 is a journal article titled, “Novel Formulation Strategies for Improving Oral Bioavailability of Drugs with Poor Membrane Permeation or Presystemic Metabolism.” (D-36.001.) The article reviews the relevant literature. Table IV is titled, “Some Examples of the Application of Ion Pairing to Increase GI Absorption.” (D-36.005.) One row in Table IV presents these elements: additives of n-alkyl sulfates, the drug trospium, the result being “increased flux,” and a citation to reference 48, which is Langguth. Actavis has cited Table IV as evidence in support of the proposition that the prior art knew that n-alkyl sulfates increased GI absorption of the QAC trospium. Plaintiffs point out that this is incorrect. Aungst 1993 is a review of literature. Table IV refers the reader to Langguth. Table IV cannot be understood to teach something contrary to the teachings of the study it cites.<sup>17</sup> Table IV correctly indicates that Langguth found that certain n-alkyl sulfates most increased the absorption of trospium. As already stated, SLS was not one of them. Aungst 1993 cannot be understood to say otherwise.

Actavis contends that the prior art did not teach away from combining SLS with MNTX. Actavis argues first that the testimony of Plaintiff’s experts on this subject does not apply to

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<sup>17</sup> Actavis argues: “Langguth describes the successful use of ion pairing with a quaternary ammonium compound, trospium, and a class of compounds known as n-alkyl sulfates, of which SLS is a member.” (D.’s Resp. Br. 17.) This is correct but incomplete. Langguth taught that n-alkyl sulfates with the chain length of SLS would not have a maximal effect with trospium, but rather would be associated with a “slight” increase in permeation. (P-254.006.) Langguth taught “successful use” only of n-alkyl sulfates with a medium chain length. (Id.)

claim 5, which does not require ion pairing. While it is correct that claim 5 does not require ion pairing, it does require, since it depends on claim 1, a formulation comprising MNTX and SLS. The key question at this point in the obviousness inquiry is whether the prior art provided a motivation to combine MNTX and SLS. Evidence of teaching away from that combination is relevant to the obviousness inquiry into both claims 2 and 5.

Actavis argues that Langguth and Kakemi do not reflect the state of the art as of the Critical Date, and that a POSA would have relied on two more recent references, Aungst 1993 and Whitehead 2007.<sup>18</sup> As already established, this Court has found that Aungst 1993 expressly cited Langguth and did not teach anything different from that reference. Whitehead 2007 studied the effects of various permeation enhancers using mannitol as a marker. (D-49.003; Tr. 582:2-4.) Plaintiffs argue that, because Whitehead 2007 did not use any QACs, it did not refute the findings of Langguth or Kakemi. Actavis does not explain why a POSA who sought to improve GI absorption of MNTX would have even looked to Whitehead 2007 for insight, much less found a motivation to combine MNTX and SLS in it. Rather, it appears that Whitehead 2007 only has relevance when viewed in hindsight – once one has found SLS and is trying to trace backwards.

“A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant.” Polaris Indus. v. Arctic Cat, Inc., 882 F.3d 1056, 1069 (Fed. Cir. 2018). Here, no reference sets out a path to combining MNTX with SLS, but the prior art directs a POSA on a path divergent to the one taken by the

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<sup>18</sup> Thus, according to Actavis, 17 years ago is recent enough, but 23 years ago is not.

patentees. The Court finds that the Kakemi and Langguth references taught away from the use of SLS to increase GI absorption of QACs, and Aungst 1993 and Whitehead 2007 do not undermine this finding.

#### **4. Unexpected results**

Plaintiffs contend that formulations embodying the claimed invention showed unexpectedly superior efficacy. “[W]hen unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art.” Kao Corp. v. Unilever United States, Inc., 441 F.3d 963, 970 (Fed. Cir. 2006). While the parties dispute whether the closest prior art is an enteric-coated oral formulation of MNTX or an immediate-release formulation, Plaintiffs contend that the invention’s immediate-release formulation with SLS show unexpected efficacy compared to both. In clinical study 1115, the formulation of the invention had a median time to laxation of .76 hours, which is almost seven hours faster or ten times faster than the immediate release tablet formulation without SLS in that study. (P-52.036, Table 9-2.) Dr. Rauck testified that this was a dramatic improvement in efficacy. (Tr. 393:10-11.) Clinical study 105 evaluated two enteric-coated MNTX formulations, and neither showed any statistically significant reduction in time to laxation. (P-40.045.) Dr. Williams stated that a POSA, prior to the critical date, would have expected SLS to have no impact on the efficacy of an oral MNTX formulation. (Tr. 473:9-20.) Plaintiffs contend that Langguth and Kakemi, the only prior art references that discussed the use of SLS with QACs, indicated that SLS did not work to increase absorption.

The clinical study evidence supports Dr. Rauck’s assessment that the inventive formulation showed a dramatic improvement in efficacy. The enteric-coated formulations in

study 105 showed no statistically significant reduction in time to laxation from predose to postdose, while the immediate release formulations without SLS in study 1115 had a median time to laxation of about 8 hours. The performance of the immediate release formulation with SLS in study 1115, with a median time to laxation of .76 hours, is markedly superior to the performance of any of the tested formulations similar to prior art oral formulations.

Dr. Chambliss opined that the performance of the inventive formulation was not unexpected. (Tr. 668:6-8.) Dr. Chambliss supported this opinion by saying that SLS was a known permeation enhancer. (Tr. 668:9-12.) There is no dispute that SLS was known in the prior art as a permeation enhancer but, in the context of the evidence of record, this is a weak argument. As discussed, Plaintiffs have cited the Langguth and Kakemi references as teaching that SLS would not be effective in increasing the absorption of MNTX. Given those references, this Court looks for evidence of teachings in the prior art that SLS would be effective in increasing the absorption of MNTX, with reason to expect a dramatic increase in efficacy. Actavis has not persuaded that a POSA would have had a reasonable basis for discounting the teachings of Kakemi and Langguth and for having an expectation that SLS would have increased the absorption of MNTX, much less with such dramatic impact.

The Court finds that formulations embodying the claimed invention showed superior efficacy to prior art formulations, both enteric-coated and immediate release. The immediate release formulations disclosed in Yuan 2000 RL are the closest prior art, but this determination is not material. Plaintiffs have shown that a POSA examining the prior art would not have expected these results, and Actavis has failed to rebut this.

The Federal Circuit has set forth these fundamental principles regarding the role of

unexpected results in the obviousness inquiry:

Secondary considerations of nonobviousness must always when present be considered, and can serve as an important check against hindsight bias. . . .

To be particularly probative, evidence of unexpected results must establish that there is a difference between the results obtained and those of the closest prior art, and that the difference would not have been expected by one of ordinary skill in the art at the time of the invention. Unexpected properties, however, do not necessarily guarantee that a new compound is nonobvious. While a “marked superiority” in an expected property may be enough in some circumstances to render a compound patentable, a “mere difference in degree” is insufficient.

And “differences in degree” of a known and expected property are not as persuasive in rebutting obviousness as differences in “kind”—i.e., a new property dissimilar to the known property. . . . When assessing unexpected properties, therefore, we must evaluate the significance and “kind” of expected results along with the unexpected results.

Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc., 752 F.3d 967, 977 (Fed. Cir. 2014)

(citations omitted). Plaintiffs argue that the superior performance of the inventive formulation, compared to the performance of prior art formulations, is a difference in kind. This Court does not agree. Faster relief from constipation does not differ in kind from slower relief from constipation; this cannot be described as a new property dissimilar to the known property. The evidence does, however, support a finding of “marked superiority:” a reduction of mean time to laxation from about 8 hours to about one hour – bringing relief ten times faster – easily supports a finding of marked superiority. This evidence of unexpected results is particularly probative of nonobviousness.

Actavis argues on several grounds that Plaintiffs have failed to demonstrate unexpected results. These arguments share a common form – they purport to show defects in Plaintiffs’

presentation – and suffer from a common problem: Actavis misapprehends the burden of proof.<sup>19</sup>

As the Federal Circuit has explained:

[The accused infringer] also asserts that [the patentee] failed to show any new and surprising result and that the Commission erred in accepting the alleged criticality of the claimed ranges. The burden of proving invalidity, however, was on [the accused infringer.] [The patentee] is under no compulsion either to prove a new and surprising result or to prove the criticality of the claimed ranges of amino acids. Rather, the burden was on [the accused infringer] to establish the lack of new and surprising results or the lack of criticality. [The accused infringer] failed to prove either.

Am. Hosp. Supply Corp. v. Travenol Labs., Inc., 745 F.2d 1, 8 (Fed. Cir. 1984). This analysis has straightforward application to the instant case. Plaintiffs bear no obligation to prove a surprising result; instead, Actavis bears the burden of proving invalidity. The Federal Circuit has provided this foundation for the obviousness inquiry:

In *Graham v. John Deere Co.*, 383 U.S. 1, 17-18, 86 S. Ct. 684, 15 L. Ed. 2d 545 (1966), and *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406, 127 S. Ct. 1727, 167 L. Ed. 2d 705 (2007), the Supreme Court set out the framework for the obviousness inquiry under 35 U.S.C. § 103:

Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented.

A determination of whether a patent claim is invalid as obvious under § 103 requires consideration of all four Graham factors, and it is error to reach a conclusion of obviousness until all those factors are considered. Objective indicia of nonobviousness must be considered in every case where present.

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<sup>19</sup> For example, Actavis writes: “Plaintiffs bear the burden of establishing that the claimed invention demonstrates unexpected properties as compared to the closest prior art.” (D.’s Resp. Br. 24.) This is contrary to well-settled Federal Circuit law.

Apple Inc. v. Samsung Elecs. Co., Ltd., 839 F.3d 1034, 1047-48 (Fed. Cir. 2016) (citation omitted). The Court applies these principles, which give Actavis the burden of proof and the Court the obligation to consider all evidence, including evidence of secondary considerations, before reaching a determination of invalidity due to obviousness.

As to Actavis' critiques of Plaintiffs' evidence of unexpected results, the Court observes that the research studies showing the performance of oral MNTX formulations in the prior art are in the record, and that it might have been a simple matter to point to a prior art result that was not left in the dust by the mean time to laxation of the inventive formulation in study 1115 – if such existed. The “Background of the Invention” section summarizes the results of a number of studies of oral MNTX formulations:

- ‘959 patent (doesn’t report data on MNTX)
- ‘591 patent [Foss ‘591] (doesn’t report laxation data)
- ’158 patent (fastest response mean time to laxation 5.2 hours)

’276 patent, col.2 ll.27-60.

The present record also includes the following studies of oral MNTX formulations:

- Yuan 1997 (D-74) (reports oral-cecal transit time, not time to laxation)
- Yuan 2000 Enteric (P-275) (reports oral-cecal transit time, not time to laxation)
- Yuan 2000 RL (D-374) (fastest response mean time to laxation 5.2 hours)
- Foss 2001 (D-40) (reports oral-cecal transit time, not time to laxation)

Defendants also cite as prior art references Sanghvi ’899 (D-44) and WO ’352 (D-73), which do not report any clinical study results. The record thus shows only one prior art oral MNTX study

which reports time to laxation, and the fastest mean time to laxation found was 5.2 hours.

Actavis itself states that Yuan 2000 RL is the only oral MNTX study in the prior art to report time to laxation data. (D.'s FOF ¶ 169.) The fastest time to laxation reported in Yuan 2000 RL was for the group administered a dose of 3mg/kg. An average 150 pound person, then, is 68 kg, and the dosage would be 204 mg. Given a rough average time to laxation of 5 hours at the 204 mg dose, what would have been the expectation of the POSA for a lower dose (150 mg) with SLS? Actavis does not articulate any reason why a POSA would have expected that a 25% reduction in dosage, formulated with SLS, would have led to an 80% reduction in time to laxation. Rather, Actavis' entire argument is contained in this sentence: "Indeed, the POSA would have had an expectation that the addition of SLS to an immediate release formulation would lead to improved efficacy because SLS was a known permeation enhancer." (D's FOF ¶ 199.) This Court, however, has already determined that the Kakemi and Langguth references taught away from the use of SLS to increase GI absorption of QACs like MNTX, and Aungst 1993 and Whitehead 2007 do not undermine this finding. In view of this determination, Actavis cannot succeed with the argument that a POSA would have expected superior results from a formulation containing SLS because of general knowledge that SLS enhanced permeation.

Furthermore, compared to the best average time to laxation observed in Yuan 2000 RL, the time to laxation for the inventive composition found in study 1115 shows marked superiority. As evidence of this, Moss 2008, reviewing Yuan 2000 RL and other studies, characterized the prior art oral formulations as having "long delays." (P-258.004.) Study 1115 found an average time to laxation for the inventive formulation of roughly 45 minutes, which is a markedly shorter delay.

Actavis also argues that Plaintiffs have failed to show that the results were unexpected compared with the closest prior art, since studies 105 and 1115 are confidential and not in the prior art. Yuan 2000 RL is in the prior art, however, and Actavis admits that it is the only prior art study of oral MNTX that reported data on time to laxation. Furthermore, Actavis states: “As Dr. Rauck explained, the clinically relevant endpoint for studies of OIC treatments is time to laxation.” (D’s Post-Trial Br. 68-69.) As just established, under well-settled Federal Circuit law, Actavis bears the burden of showing the lack of unexpected results. The argument that the proper study for comparison is one which supports a finding of unexpectedly superior efficacy on the clinically relevant endpoint does not help Actavis meet that burden.

The Court finds that the performance of the inventive formulation, as reported in study 1115, is markedly superior to that of any oral formulation for which time to laxation data is available in the prior art. Actavis has not shown that any prior art formulation came anywhere close to the performance of the inventive formulation. Thus, when Actavis asserts that “plaintiffs’ evidence of unexpected results must fail,” that is the incorrect legal conclusion: it is Actavis that has failed to establish the lack of unexpected results.<sup>20</sup> (D.’s Resp. Br. 22.)

Plaintiffs have established that the superior performance of the inventive formulation was unexpected. “[W]hen a patent simply arranges old elements with each performing the same function it had been known to perform and yields no more than one would expect from such an

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<sup>20</sup> In Eurand, Inc. v. Mylan Pharms., Inc. (In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.), 676 F.3d 1063, 1075 (Fed. Cir. 2012), the Federal Circuit acknowledged that some confusion on this issue was understandable, in view of the Court’s precedent. The Court stated clearly, however, that the burden of proof never shifts to the patentee in the obviousness inquiry. Id. at 1079. “[T]he Supreme Court has never imposed nor even contemplated a formal burden-shifting framework in the patent litigation context.” Id. at 1077.

arrangement, the combination is obvious.” KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 417 (2007). Plaintiffs have shown, and Actavis has failed to rebut, that the combination of MNTX and SLS in an oral formulation yielded much more than one would have expected from such an arrangement, based on the prior art. Secondary considerations of non-obviousness may often be the most probative and cogent evidence of non-obviousness in the record. P&G v. Teva Pharm. USA, Inc., 566 F.3d 989, 998 (Fed. Cir. 2009).

In conclusion, Defendant’s obviousness theory has at least two large holes. The first hole is the failure to establish the fundamental proposition that the prior art believed that MNTX had poor permeability such that it was a problem to be solved. The second hole is the failure to show how it would have been obvious to the POSA, following the teachings of Table 1 of Aungst 1993, to select SLS to combine with MNTX in an oral formulation. Lastly, Plaintiffs have shown, and Actavis has not disproven, that the prior art taught away from the inventive formulation, and that the inventive formulation produced unexpected results, supporting a conclusion of nonobviousness.

“An inference of nonobviousness is especially strong where the prior art’s teachings undermine the very reason being proffered as to why a person of ordinary skill would have combined the known elements.” Depuy Spine, Inc. v. Medtronic Sofamor Danek, Inc., 567 F.3d 1314, 1326 (Fed. Cir. 2009). Such is the case here. Actavis contends that the Accordingly Phrase demonstrates that “the prior art that the inventors described in the Background of the Invention section taught the need for more bioavailable oral dosage forms of MNTX.” (D.’s FOF ¶ 40.) This Court has determined that the prior art evidence of record in this case taught that more bioavailable (in the sense of availability in the blood plasma) oral dosage forms of

MNTX were not needed and, furthermore, that they were undesirable. These teachings undermine the very reason being proffered as to why a person of ordinary skill would have combined the known elements. This makes the inference of nonobviousness especially strong.

Actavis' obviousness case unsuccessfully tries to bridge the gap between the teachings of the prior art about oral formulations of MNTX to treat OIC and the inventive formulation. In largest part, Defendant has tried to build this bridge on the pillars of the Accordingly Phrase and the Aungst 1993 reference. Actavis contends that the Accordingly Phrase should be interpreted as an admission by the inventors that the prior art recognized the need to increase the bioavailability of MNTX in oral formulations, and that Aungst 1993 taught that bioavailability may be increased by the use of permeation-enhancing excipients. A known problem is thus connected to a known solution, Actavis argues. There are two main defects in this argument. First, the Accordingly Phrase is ambiguous and, in any case, neither the Accordingly Phrase nor the '276 patent contradict the teachings of the prior art that low bioavailability was an advantageous property of oral MNTX, rather than a problem. Contrary to Defendant's thesis, the prior art did not teach that low bioavailability was a problem to be solved. Second, Aungst 1993 teaches the use of permeation-enhancing excipients as a possible solution only to problems of bioavailability. Actavis proposes that the POSA would consider low bioavailability to be a problem to be solved and, therefore, would look to Aungst 1993 in the quest for a solution, but the evidence does not support this. Because the evidence shows that the prior art taught that bioavailability was unrelated to an oral MNTX formulation's efficacy, and that increasing plasma levels was undesirable because of the risk of side effects, Aungst 1993 fails to be relevant to the search of the hypothetical POSA wanting to improve on the efficacy of prior art oral

MNTX formulations. Aungst 1993 can serve as a connector in Actavis' theory only if Defendant's interpretation of the Accordingly Phrase is correct, but it is not. Actavis has thus failed to connect the teachings of the prior art to the inventive use of a permeation-enhancing excipient. Without this essential bridge, Actavis has failed to show an obvious path to the invention.

Actavis has failed to prove that independent claim 1 of the '276 patent is invalid as obvious. Because claims 2 and 5 depend on claim 1, Actavis cannot prove that claims 2 and 5 are obvious. Actavis has failed to prove that claims 2 or 5 are invalid for obviousness.

## **B. Infringement of claim 2**

The parties stipulated to a finding of infringement of claim 5, and so only the question of infringement of claim 2 is at issue. The parties do not dispute that Actavis' proposed ANDA product contains MNTX and SLS in quantities that meet the limitations of independent claim 1. The question of infringement of claim 2 turns on the question of whether Plaintiffs have proven, by a preponderance of the evidence, that the MNTX and SLS in the proposed ANDA product "form an ion pair when dissolved in solution," as required by claim 2.

Plaintiffs offered the testimony of Dr. Koleng, who oversaw a series of chemical tests on the ANDA product and a related mixture. Plaintiffs argue that this evidence is sufficient to prove, by a preponderance of the evidence, that it is more likely than not that the MNTX and SLS in the proposed ANDA product form an ion pair when dissolved in solution.

Dr. Koleng testified about three experiments which were executed by commercial laboratory SSCI. The shake-flask method was used to determine the APC of MNTX in

solution.<sup>21</sup> In the first experiment, an APC of approximately 1.0 was found for three ANDA product samples, and an APC of .002 for MNTX bromide alone. (P-164.004.) In the second experiment, SSCI created a tablet blend which, Plaintiffs contend, duplicated the ingredients in the ANDA product, but without SLS, and found an APC of .01. (P-165.004.) In the third experiment, SSCI repeated the shake-flask procedure with two product samples, but then measured not the APC but the concentrations of MNTX and SLS in the octanol layer, and found that MNTX and SLS were present in a 1:1 molar ratio. (Tr. 101:3-12.) Plaintiffs contend that this evidence proves that that the MNTX and SLS in the proposed ANDA product form an ion pair when dissolved in solution.

Actavis argues that the experiments do not prove infringement of claim 2 on several grounds. First, Actavis contends that ion pairing is not the only explanation for why the APC of MNTX in the proposed ANDA product might show an increase. Actavis contends that another possible explanation is the Galvani potential difference. In support, Actavis cites the testimony of Plaintiffs' expert, Dr. Davies, and two journal articles, Lombardo 2008 and Bouchard 2001. In short, the cited evidence does not support Actavis' contention. In the cited testimony, Dr. Davies made clear that the Galvani potential difference theory "only applies with an excess of the anion present." (Tr. 352:3-7.) Dr. Davies repeated this and stated: "it's only applicable . . . to cases where there's an excess of the anion, which we don't have." (Tr. 347:19-21.) He further explained that the Lombardo and Bouchard references dealt with the situation in which an excess of the anion was present. (Tr. 352:2-7.) Dr. Davies also testified:

Q. Are you offering the opinion to this Court that the only possible explanation for the increase in apparent partition coefficient in Example 4 is due

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<sup>21</sup> For convenience, the Court may refer to "the APC" as shorthand for "the APC of MNTX."

to ion-pairing?

A. It's a standard way to show that you have ion-pairing. A person of ordinary skill would use this to demonstrate that they have not ion-pairs. I can't think of any other explanation for why you would get an increase in apparent partition coefficient.

(Tr. 342:18-25.) Dr. Davies thus clearly did not, as Actavis claims, testify that the Galvani potential difference is another possible explanation for an increase in APC as observed in the context of this case. To the contrary, he stated clearly that ion pairing was the only explanation he could think of for an increase in APC as observed in this case. Dr. Davies also explained that an increase in measured APC shows that ion pairing has occurred. (Tr. 317:4-15.)

Actavis also cites the testimony of Dr. Williams in support of the proposition that an increase in APC does not demonstrate ion pairing. Dr. Williams did indeed agree that the '276 patent leaves open whether or not the explanation for the increase in APC is due to the formation of ion pairs. (Tr. 506:16-20.) Dr. Williams was not, however, asked to explain his opinion on this point, and the Court does not find it to be consistent with the teachings of the '276 patent.

For example, the specification states:

In certain embodiments, the excipient increases the lipophilicity of methylnaltrexone by forming an ion pair with cationic methylnaltrexone. Ion pairing increases the partitioning of methylnaltrexone into an organic phase such as a lipid bilayer. In certain embodiments, the excipient forms an ion pair with methylnaltrexone such that when the composition is in solution, the methylnaltrexone has an apparent octanol/water partition coefficient of at least 0.25 at a pH between 1 and 4.

'276 patent, col.14 ll.21-29. This is a very clear statement that, in certain embodiments, ion pairing results in an increase in measured APC of MNTX. This Court does not see how it leaves the explanation open.

Actavis also cites similar testimony from Dr. Williams:

Q. But in your view, there are possibly other mechanisms responsible for the increase in apparent partition coefficient other than ion-pairing, right?

A. Based on the patent, yes.

(Tr. 507:2-5.) This interchange is best described as cryptic: it is entirely unclear what Dr. Williams meant, but it seems likely that he was giving some kind of qualified response which received no further investigation. In light of the fact that Dr. Williams was neither offered nor qualified as an expert in chemistry, but rather as a formulator, as well as the inconclusive nature of this testimony, the Court finds that it does not significantly weaken the conclusions of Dr. Davies.

Actavis also cites inconsistency in Dr. Koleng's testimony on whether an increase in APC is necessarily due to ion pairing. As Actavis contends, Dr. Koleng admitted that he had no experience with ion pairing and that he did not consult any scientific literature on ion pairing to educate himself on the subject. (Tr. 108:17-109:11.) His statements about ion pairing will be given no weight.

In sum, Actavis cites the testimony of Drs. Koleng, Davies, Chambliss and Williams in support of the proposition that an increase in APC does not demonstrate ion pairing. Dr. Koleng's testimony is given no weight. The cited testimony of Dr. Chambliss is only a conclusory statement that there are other explanations, without giving any other possible explanations.<sup>22</sup> The testimony from Dr. Williams is unsupported by the patent, too cryptic to be interpreted with confidence, and outside the domain of his expertise as a formulator. Lastly, Dr. Davies' testimony does not support the proposition, but rebuts it. The Court found Dr. Davies

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<sup>22</sup> Actavis does not here cite Dr. Chambliss' carrying theory as a possible explanation, which will be addressed below.

to be an impressive, highly credible expert in his field. His credentials are sterling, his testimony was cogent and persuasive, and this Court gives it great weight. This Court finds that Plaintiffs have shown by a preponderance of the evidence that ion pairing is the only possible explanation for the increase in the APC of MNTX observed in Plaintiffs' experiments.

Actavis next argues that APCs cannot be determined for ingredients within tablets. In support, it points to the testimony of Dr. Chambliss and the deposition testimony of Dr. Diorio, one of the inventors. As Actavis contends, Dr. Chambliss and Dr. Koleng agreed that neither knew of any report in the literature in which the shake-flask method was used to determine an APC in a tablet, as opposed to a pure compound.

While Actavis' post-trial brief clearly contends that APCs cannot properly be determined for tablets, it never states any underlying principle to support this. What exactly is the problem with using the shake-flask method to determine the APC of MNTX in a tablet? At some points, Actavis suggests that skilled artisans determine APCs of pure compounds, never stating, however, that this is a limiting rule. It is clear, however, that such cannot be the case, since the '276 patent specification states: "The composition includes methylnaltrexone and an amphiphilic pharmaceutically acceptable excipient that form an ion pair or salt with methylnaltrexone when dissolved in solution, thereby increasing the octanol/water partition coefficient of methylnaltrexone." '276 patent, col.5 ll.62-66. This requires that an APC can be determined for a composition of MNTX and an excipient. Since that is clearly a predicate for that patent disclosure, what exactly is the line that Actavis proposes? Why would it be proper to use the shake-flask method to determine the APC of MNTX in some compositions, such as the one cited in the specification, but not tablet compositions? Actavis has no explanation, save for Dr.

Chambliss' carrying theory, which will be discussed further below.

Actavis next points to the fact that there is only one example of the shake-flask method in the '276 patent, and that it was performed on a pure compound, not tablets. This refers to Example 4, which discloses determination of the APC through use of the shake-flask method with three MNTX salts. '276 patent, col.31 ll.28-46. This argument is not persuasive. Actavis does not contend that Example 4 was intended to be a comprehensive and exclusive set of rules for determination of APCs using the shake-flask method. Example 4 is, as the patent states, an example.<sup>23</sup> It describes one particular use of one method to determine APCs for three MNTX salts. As will be discussed further below, the specification expressly states that a number of procedures may be used to determine APC.

Actavis cites the excerpted deposition testimony of Dr. Diorio, who stated that he did not know how to measure the partition coefficient of MNTX in a composition, or whether one could determine the partition coefficient of MNTX in a composition. (D-380, Diorio Tr. 126:7-20.) Without more, the Court cannot assess what this means. The Court has no way to know whether this means that Dr. Diorio has no expertise in the details of APC measurement procedures, or something else. Was he a clinician and not a chemist? Given that the '276 patent specification teaches the measurement of APCs in compositions, this testimony does not appear to be significant.

Actavis also cites the testimony of Dr. Chambliss, who did state that he believed that Dr. Koleng's use of the APC measurement was not proper. The weight to be given to this testimony

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<sup>23</sup> Furthermore, the specification states: "*Exemplary* methods for the determination of apparent octanol/water partition coefficient of methylnaltrexone salts are described in the Examples below." '276 patent, col.14 ll.13-15 (italics added.)

must be reduced because of the lack of support Dr. Chambliss offered. Dr. Chambliss stated: "I don't think you can use this test to determine the partition coefficient, and then you cannot infer from that that it's ion pairing. You don't know why a drug has gone from one phase to the other." (Tr. 154:4-8.) This one aspect of his opinion could have merit: a finding that the APC of MNTX in a composition with multiple excipients changed may leave questions about the reason for the change. But it was Dr. Chambliss' attempt at explanation of this opinion that was unpersuasive:

Q. What's the significance of the fact that some of the excipients are insoluble in the Actavis's ANDA product?

A. Well, if you just took this and made a simple blend, and you're going to have about 40 percent of it is insoluble. So you drop that in a solution, it's just going to be floating around. So when you shake it, it's just going to be from one phase to the other phase.

Q. So in your opinion, would the presence of these excipients impact in any way the results from a shake-flask test performed on the Actavis's ANDA product in solution?

A. I think you would expect that it definitely could. It's -- it is -- as the material is floating around, and we are going to talk about the manufacturing process just in a second, it could be carrying the active ingredient with it from one phase to the other. It has nothing to do with ion pairing.

(Tr. 156:15-157:5.) The only explanation that Dr. Chambliss gave for his opinion that using the shake-flask method with the ANDA product was improper concerned the role of the insoluble excipients. According to Dr. Chambliss, because they are insoluble, they float around, going from one phase to the other. Dr. Chambliss speculates that, in that process, an insoluble excipient might "carry" the active ingredient from one phase to the other. Actavis has not shown that the theory has any relevance to the issues before the Court. The carrying theory proposes that insoluble excipients carry MNTX from the aqueous phase into the octanol phase. It would appear that the design of the first and second experiments controls for that. The

compositions tested contained the same insoluble excipients. Actavis has argued only that the manufacturing process differed (plus, of course, the presence or absence of SLS.) There is no reason to believe that the effect of “carrying,” if any, would not be the same in the two tests, since the test material had the same insoluble components in both. The carrying theory has no power to explain the difference between the measured APCs in the first and second experiments.

The Court finds that Dr. Chambliss’ opinions about the use of the shake-flask method to measure the APC of MNTX in a composition deserve weight only in part. Dr. Chambliss raised a question which has value: if one observes a change in the APC of MNTX in a composition, how does one account for the change with confidence, given the presence of multiple excipients? This question will be explored in detail below. As for Dr. Chambliss’ carrying theory, the Court finds that it is unsupported by the evidence of record, and the Court will give it no weight. The evidence of record does not support the proposition that Plaintiffs’ experimental evidence is invalid because the APC of a compound in a tablet composition cannot be validly determined. The ’276 patent specification clearly teaches the measurement of APCs in compositions, and Actavis has offered no persuasive explanation of why this cannot apply to tablets.

Actavis next challenges Plaintiffs’ reasoning about the interpretation of the results of the three experiments with two arguments. First, Actavis challenges the comparison of the APC for a tablet, from the first experiment, with the APC for the loose tablet blend without SLS, from the second experiment. Actavis argues that the presence of SLS is not the sole difference between the tested materials: the tablet had undergone a manufacturing process, while the loose tablet blend had not undergone that manufacturing process. This is factually correct, but it is not sufficient to show that Plaintiffs’ analysis is invalid. Actavis points out that, under these

circumstances, the difference in APC could be due to the difference in manufacturing process, rather than the presence of SLS in the formulation. While this is a valid point, without more, it raises no more than a metaphysical doubt. Actavis has offered no evidence that the difference in manufacturing process *would* have changed the measured APC of MNTX.<sup>24</sup> Nor has it offered any viable theory for why that might be the case. All that it has offered are the vague and unsupported speculations of Dr. Chambliss that it might have. While it may be true that differences in the manufacturing process could hypothetically account for the differences in measured APC, Actavis has presented no basis, save for the speculations of Dr. Chambliss, to find that this is the case.

Second, Actavis challenges Plaintiffs' reasoning about the third experiment. Actavis observes, correctly, that the third experiment did not assess the levels of excipients other than SLS in the octanol phase, and so another excipient might have also had a 1:1 molar ratio with MNTX. This appears to be a fragment of an argument, and the Court does not discern its significance.

Actavis next argues that the SSCI test results are unreliable because "they differed dramatically from what was disclosed in the '276 patent." (Pls.' FOF ¶ 91.) Actavis points to the fact that SSCI reported an APC for MNTX bromide of .002, while the patent reports an APC for MNTX of .025. Actavis does not address the fact that Example 4 in the patent does not state that .025 is the APC for MNTX bromide, but says only that it is for MNTX. '276 patent, col.31 1.45. The table in Example 4 discloses that three different MNTX salts had vastly different

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<sup>24</sup> As Plaintiffs note, given that the shake-flask method involves putting the tested material in solution, what are the physical and chemical transformations produced by manufacturing that are not undone by dissolving?

APCs – from roughly 2 to 32. '276 patent, col.31 ll.50-55. Actavis has not persuaded that there is any significance to the fact that the APC for MNTX bromide that SSCI reported differs from the APC for unspecified MNTX stated in the patent.

Furthermore, the specification contains an express definition of “apparent partition coefficient,” which, *inter alia*, states:

The apparent partition coefficient may be determined under various conditions, for example, temperature, pH, concentration, etc. . . The apparent partition coefficient of a compound may be determined by procedures known in the art, for example, in the U.S. Pharmacopeia. The apparent partition coefficient may be determined by the procedure used to determine the apparent partition coefficients of methylnaltrexone dodecyl sulfate and methylnaltrexone heptyl sulfate in the Examples.

'276 patent, col.10 ll.27-40. Note that the specification makes two statements about the procedures to be used for determination of the APC, and that both use the phrase, “may be determined by.” Note as well that the first statement specifies the plural, “procedures.” This indicates that the method to be used to determine the APC is not limited to one particular method.

Note as well that the patentees observed that the APC may be determined under various conditions. This fits with the testimony of Dr. Davies:

Q. Why is it important in an apparent partition coefficient experiment to know how much anion and cation are present in solution?

A. Because, as I've mentioned, the relative ratios will change the partition coefficient that you measure.

(Tr. 318:8-12.) Dr. Davies stated that changes in the relative ratio of concentrations will change the APC. Dr. Williams agreed that APC values can vary with pH. (Tr. 507:10-20.) All of this evidence supports the inference that a particular compound has no absolute APC value, and that the measured APC for a particular compound may vary based on a number of conditions,

including testing method used, relative concentration ratio, and pH.

Actavis next argues that Dr. Elder's test results show that there was no ion pairing. As noted, stipulated fact number 76 states that Dr. Elder attempted to replicate SSCI's APC measure of MNTX in the ANDA tablets in solution at a different pH and obtained measurements of approximately .05. Actavis contends that this shows that the MNTX and SLS will not form ion pairs at a pH of 1. Dr. Chambliss testified that this shows that the ANDA product does not infringe claim 2. (Tr. 172:20-23.) This argument is problematic. The premise of Dr. Elder's testing is that pH changes the APC measured. Dr. Elder's testing is evidence that, indeed, the pH changed the APC measured, but the Court has no evidence about how to interpret that change given that SSCI's other measurements were all at a different pH. There is no evidence that Dr. Elder also determined the APC of MNTX bromide at pH 1.1. Because APC values vary based on many conditions, including pH, the statement that a particular value was obtained at a particular pH does not, without more, support any inference about ion pairing. Dr. Elder's APC measurement of MNTX in the ANDA tablet does not support any inference about the presence or absence of ion pairing. Dr. Elder's experiment confirmed what is undisputed: pH affects measured APC.

Actavis next argues that Plaintiffs have offered no evidence that the Actavis ANDA product will infringe when it is used by patients, as the issue is what will happen after patients have ingested the tablet and it is in the stomach. This argument is a non-starter.<sup>25</sup> Claim 2

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<sup>25</sup> In support, Actavis cites Biovail Corp. Int'l v. Andrx Pharm., Inc., 239 F.3d 1297, 1299 (Fed. Cir. 2001), which is inapposite. The claim at issue in Biovail included this limitation: "ensuring that the solubility of the Diltiazem is unaffected by the pH of the gastrointestinal tract or other adverse conditions which the composition will meet therein . . ." Id. In the instant case, claim 2 contains no similar limitation.

covers a composition, not a treatment method, and it requires that the MNTX and SLS “form an ion pair when dissolved in solution.” No one contends that the SSCI testing did not involve dissolving the composition in solution. Actavis’ argument here seeks to import new limitations into claim 2, which is not limited to solutions found within the human GI tract. This is highlighted by the specific pH limitations disclosed in dependent claim 8.

This Court has considered Actavis’ challenges to Plaintiffs’ infringement case and has rejected everything but one point, which is the general caution that changes in the APC of MNTX in a composition with multiple excipients may leave questions about the explanation for the change. With that in mind, the Court considers the SSCI experiments.

SSCI measured the APC of MNTX in the ANDA product as approximately 1.0, the APC of MNTX bromide alone as .002, and the APC in the tablet blend without SLS as .01. Actavis has failed to persuade the Court that the fact that the tablet blend had not undergone the same manufacturing process as the tablet materially impacted these results. Plaintiffs have presented unrefuted evidence that, when SLS is removed from the tablet blend, the measured APC drops substantially. The Court has determined that, in the context of this case, the only explanation for this change is the presence or absence of ion pairing. Plaintiffs have also presented unrefuted evidence that the MNTX and SLS in the ANDA tablet, dissolved in solution, appear in the octanol phase in a 1:1 molar ratio. This supports the inference that the MNTX and SLS have formed ion pairs. Actavis has presented no useful experimental evidence.

Actavis has, at best, persuaded that the SSCI testing is not the perfect testing for an airtight scientific case. The evidentiary standard here is not, however, beyond a reasonable doubt: it is a preponderance of the evidence standard. Actavis has not persuaded that the

possible imperfections in the SSCI testing render it valueless as evidence. Furthermore, Actavis has not persuaded that any of the imperfections substantially reduces the weight this Court should give to the SSCI test evidence. Actavis could have conducted tests which demonstrated that, when its ANDA product is in solution, the MNTX does not ion pair with SLS, but it did not.<sup>26</sup>

The Court finds that Plaintiffs' evidence of infringement deserves significant weight. Plaintiffs have presented experimental evidence that the APC of MNTX in the ANDA tablet is significantly greater than the APC of MNTX in the tablet blend without SLS. The tablet blend experiment is not the perfect control, since, as Actavis contends, the tablet blend has not undergone the tablet manufacturing process. Actavis did not present, however, any basis to find that the manufacturing difference can account for the difference in APC value. The only evidence to the contrary was the opinion of Dr. Chambliss, which the Court found unsupported and unpersuasive. The Court concludes that the observed difference in the APC of MNTX between the ANDA tablet and the tablet blend without SLS is explained solely by the presence and absence of SLS. There is no evidence that other excipients played any role. The Court also concludes that the observed increase in APC value can only be accounted for by the formation of ion pairs between MNTX and SLS.

Actavis presented the opinion of Dr. Chambliss that the shake-flask method could not be used on a tablet composition, but, again, the Court finds the opinion of Dr. Chambliss to be

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<sup>26</sup> The Court recognizes that the accused infringer does not bear the burden of proof and is not suggesting that Actavis carries any burden here. The Court does, however, weigh the evidence in the record before it, and an accused infringer may choose to present rebuttal evidence. The only experimental evidence Actavis has offered in rebuttal is the testing by Dr. Elder which this Court has determined has little relevance to what is at issue.

unsupported and not persuasive. At most, Actavis persuaded this Court that the presence of multiple excipients requires caution in interpretation, as well as adequate experimental control, to have confidence in the inference that the addition or removal of one particular excipient accounts for observed changes in APC. The Court finds that Plaintiffs' experiments adequately controlled for the presence of multiple excipients, and that, in view of the applicable evidentiary standard, the experimental evidence supports the inference that it is more likely than not that the presence or absence of SLS alone accounts for the difference in APC measurements.

The Court concludes that Plaintiffs have proven, by a preponderance of the evidence, that the MNTX and SLS in the Actavis ANDA product form an ion pair when dissolved in solution. Plaintiffs have proven, by a preponderance of the evidence, that the proposed ANDA product will infringe claim 2. Actavis has failed to prove, by clear and convincing evidence, that claims 2 or 5 of the '276 patent are invalid as obvious. Judgment will be entered in favor of Plaintiffs on their claims that the proposed ANDA product infringes claims 2 and 5 of the '276 patent.

Pursuant to FED. R. CIV. P. 52(a), the Court presents its findings of fact and conclusions of law.

## **FINDINGS OF FACT**

- I. This Opinion incorporates by reference all stipulated facts set forth in the Final Pretrial Order.
- II. Based on the evidence presented at trial, this Court now makes the following findings of fact:
  1. The '276 patent descends from provisional application No. 61/313,018, filed on March 11, 2010 (the "Critical Date.")
  2. MNTX was known in the prior art as an opioid receptor antagonist useful for the

treatment of OIC. An MNTX formulation for subcutaneous administration was FDA-approved. Researchers had published articles teaching various oral MNTX formulations, including tablets.

3. SLS was known in the prior art both as a pharmaceutical excipient and as a permeation enhancer.
4. Bioavailability of a drug is the extent to which the drug reaches the blood plasma and has systemic availability.
5. Permeability of a drug is the extent to which an orally administered formulation is absorbed into the intestine, prior to exposure to intestinal metabolism.
6. The primary clinical endpoint and thus measure of efficacy in the treatment of OIC is time to laxation, and the prior art recognized that lower time to laxation is better.
7. An orally-administered drug with high potency can elicit a pharmacologic response even if it has low permeability.
8. The Yuan 1997 prior art reference taught that MNTX had lower lipid solubility than fairly lipid soluble compounds like naltrexone.
9. The prior art understood orally-administered MNTX to have lower permeability than naltrexone.
10. The Yuan 2000 RL prior art reference taught that an orally-administered immediate release formulation of MNTX, at a dosage of 3.0 mg/kg, resulted in an average time to laxation of roughly 5 hours. This is the only study in the prior art that reported time to laxation data.
11. The prior art did not recognize the lower permeability of orally-administered MNTX, relative to compounds like naltrexone, as a problem to be solved.
12. Dr. Chambliss' testimony that the prior art viewed the lower permeability of orally-administered MNTX as a problem to be solved was not supported by the prior art references of record, and his testimony on this subject was given no weight.
13. The prior art knew that orally-administered MNTX produced low plasma levels of the drug.
14. The prior art knew that MNTX acted locally in the GI tract and that efficacy in treating OIC was unrelated to bioavailability.

15. The prior art recognized that higher plasma levels of MNTX increased the risk of side effects such as orthostatic hypotension.
16. The Yuan 2000 Enteric study tested an oral enteric formulation designed to achieve lower plasma levels of MNTX.
17. The prior art recognized that, due to the increased risk of side effects, increasing bioavailability of orally-administered MNTX was undesirable.
18. A prior art POSA would not have been motivated to improve the permeability of orally-administered MNTX.
19. A prior art POSA would not have been motivated to improve the bioavailability of orally-administered MNTX.
20. A prior art POSA would have been motivated to design an oral MNTX formulation that minimized plasma levels and therefore bioavailability.
21. There is no evidence that the prior art was concerned about the cost of manufacturing MNTX.
22. Table 1 in the Aungst 1993 reference deals with oral pharmaceutical bioavailability problems and potential solutions. The Aungst reference states that Table 1 categorizes the most common causes of poor oral bioavailability. One listed cause is “poor membrane permeation,” with three subcategories: poor partitioning, low diffusivity, and binding to mucus or membrane. Actavis did not argue that any of the subcategories applied to oral MNTX. Table 1 lists five possible solutions for poor membrane permeation: permeation enhancers, ion pairing, complexation, and lipid or surfactant vehicles.
23. Table IV in the Aungst 1993 reference presents examples of the application of ion pairing to increase GI absorption. One entry in Table IV lists n-alkyl sulfates with the drug trospium citing to reference 48, which is the Langguth reference.
24. A POSA reading Table IV would read the underlying studies it cites. A POSA would not understand the relevant entry in Table IV to teach something different from what Langguth taught.
25. A POSA desiring to improve the permeability of an oral MNTX formulation, while minimizing blood plasma levels of MNTX, would not have found Table 1 relevant or helpful. A POSA desiring to improve the permeability of an oral MNTX formulation, while minimizing blood plasma levels of MNTX, would not have found the Aungst 1993 reference to be relevant or helpful.

26. The prior art knew of a large number of compounds that could function as GI permeation enhancers.
27. The Chambliss List is the creation of Dr. Chambliss and does not appear in any prior art reference of record.
28. The record contains no evidence of how many compounds known in the prior art meet all the criteria in the Chambliss List.
29. MNTX is a compound in the chemical genus of quaternary ammonium compounds (“QACs.”)
30. SLS is a compound in the chemical genus of n-alkyl sulfates. SLS has a chain length of 12.
31. A POSA working on oral MNTX formulations would look to prior art references dealing with QACs.
32. The Kakemi reference disclosed research on the effect of SLS on rectal absorption of poorly absorbable compounds, including three QACs. Kakemi states that no absorption of strong QACs could be detected.
33. The Langguth reference disclosed research on the effect of various counterions, including n-alkyl sulfates, on the permeation of the QAC trospium across rat intestine and human abdominal epidermis. Langguth reported that counterions with a chain length of 7 or 9 had maximum effect on permeation of trospium. N-alkyl sulfates with a chain length of 12 were associated with permeation levels that were only slightly different from that of trospium alone.
34. A POSA, reading the Kakemi reference, would be discouraged from using SLS to improve GI absorption of a QAC.
35. A POSA, reading the Langguth reference, would be discouraged from using an n-alkyl sulfate with a chain length of 12 to improve GI absorption of a QAC, and would be encouraged to use an n-alkyl sulfate with a chain length of 7 or 9 for that purpose.
36. The Whitehead 2007 reference studied the effects of various permeation enhancers on mannitol. A POSA concerned with the permeation of oral MNTX would not find Whitehead helpful or relevant.
37. The only prior art oral MNTX clinical study to report time to laxation data is Yuan 2000 RL, which reported an average time to laxation of its highest dosage

group of roughly 5 hours.

38. Study 1115 reported an average time to laxation for the inventive formulation of .76 hours.
39. The inventive formulation was found to provide markedly superior performance, based on time to laxation, compared to the prior art.
40. In view of the Kakemi and Langguth references, which taught that SLS would not be effective in increasing permeation of MNTX, these results would not have been expected by a prior art POSA.
41. Actavis' proposed ANDA product meets the limitations of claim 1.
42. SSCI measured the APC of MNTX in the Actavis ANDA product and in a composition with the same ingredients as the ANDA product, minus SLS. The APC of MNTX in the ANDA product was roughly one hundred times the APC of MNTX in the composition without SLS.
43. The only possible explanation for the difference in these measurements of the APC of MNTX is ion pairing between MNTX and SLS.
44. When the Actavis ANDA product is dissolved in solution, ion pairing of MNTX and SLS occurs.
45. Actavis' proposed ANDA product meets all the limitations of claim 2.

## **CONCLUSIONS OF LAW**

1. This Court has jurisdiction over this case pursuant to 28 U.S.C. § 1331.
2. The parties accept this Court's personal jurisdiction.
3. Venue is proper in this district pursuant to 28 U.S.C. § 1391(b).
4. "A patent shall be presumed valid. Each claim of a patent (whether in independent, dependent, or multiple dependent form) shall be presumed valid independently of the validity of other claims; dependent or multiple dependent claims shall be presumed valid even though dependent upon an invalid claim. The burden of establishing invalidity of a patent or any claim thereof shall rest on the party asserting such invalidity." 35 U.S.C. § 282.
5. All the elements of claim 1 were known in the prior art.

6. The Accordingly Phrase in the '276 patent is ambiguous and, beyond being a general statement of a need to improve efficacy, does not characterize the state of the prior art.
7. The specification of the '276 patent states that, in certain embodiments, an amphiphilic excipient increases the lipophilicity of MNTX, which results in an increase in permeation.
8. The Chambliss List selects and combines diverse elements drawn from the prior art without establishing the reasons to select and combine them, contrary to the requirement under Federal Circuit law that “a skilled artisan would have had reason to combine the teaching of the prior art references to achieve the claimed invention.” Par Pharm., Inc. v. TWi Pharm., Inc., 773 F.3d 1186, 1193 (Fed. Cir. 2014).
9. Actavis has failed to prove, by clear and convincing evidence, that a prior art POSA would have been motivated to improve the permeability of MNTX in an oral formulation.
10. Actavis has failed to prove, by clear and convincing evidence, that it would have been obvious to a prior art POSA to combine MNTX and SLS in a tablet formulation.
11. The prior art taught away from combining MNTX and SLS in a tablet formulation.
12. The inventive formulation produces markedly superior efficacy compared to the prior art, which is an unexpected result.
13. The secondary considerations of teaching away and unexpected results support the conclusion that claims 2 and 5 are nonobvious.
14. Actavis has failed to prove, by clear and convincing evidence, that claims 2 and 5 are invalid as obvious, pursuant to 35 U.S.C. § 103.
15. Claims 2 and 5 of U.S. Patent No. 8,524,276 are valid patent claims.
16. Plaintiffs have proven, by a preponderance of the evidence, that the Actavis ANDA product infringes claim 2.
17. The Actavis ANDA product infringes claim 5.

An appropriate Order follows.

s/ Stanley R. Chesler  
Stanley R. Chesler, U.S.D.J.

Dated: July 17, 2019